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Complete List of Authors:	Keating, Dolores; Saint John of God Hospitaller Services, Pharmacy Department; Royal College of Surgeons in Ireland, School of Pharmacy McWilliams, Stephen; Saint John of God Hospital Boland, Fiona; Royal College of Surgeons Ireland, 123 St Stephens Green, HRB Centre For Primary Care Research, Division of Population Health Sciences (PHS) Doyle, Roisin; 6DETECT Early Intervention in Psychosis Service, Blackrock, Co Dublin, Ireland Behan, Caragh; Cluain Mhuire Services, Newtownpark Avenue, Blackrock, Co Dublin Strawbridge, Judith; Royal College of Surgeons in Ireland, School of Pharmacy Clarke, Mary; DETECT Early Intervention in Psychosis Service
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Prescribing Pattern of Antipsychotic Medication for First Episode Psychosis: A Retrospective Cohort Study

Dolores Keating PhD[1,2], Stephen McWilliams MD[3,4], Fiona Boland PhD[5], Roisin Doyle MSc[6], Caragh Behan PhD[7], Judith Strawbridge PhD[2] and Mary Clarke MD [4,6]

Corresponding author:

Dr Dolores Keating, [1]Pharmacy Department, Saint John of God Hospital, Stillorgan, Co Dublin, Ireland;

[2]School of Pharmacy, Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin 2.

Tel +35312771607. Email Dolores.keating@sjog.ie

Co-authors

Dr Stephen McWilliams, [3]Saint John of God Hospital, Stillorgan, Co Dublin, Ireland

[4]School of Medicine, University College Dublin, Dublin 4.

Dr. Fiona Boland, [5]HRB Centre for Primary Care Research, Department of General Practice, Royal College of Surgeons in Ireland, 123 St Stephens Green, Dublin 2, Ireland

Roisin Doyle, [6]DETECT Early Intervention in Psychosis Service, Blackrock, Co Dublin, Ireland

Dr Caragh Behan, [7]Cluain Mhuire Services, Newtownpark Avenue, Blackrock, Co Dublin

Prof Judith Strawbridge, [2]School of Pharmacy, Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin 2.

Prof Mary Clarke, [6]DETECT Early Intervention in Psychosis Service, Blackrock, Co Dublin, Ireland

[4]School of Medicine, University College Dublin, Dublin 4.

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ABSTRACT

Background

Initial experience of antipsychotic medication is crucially important for patients with implications for service engagement and treatment outcomes. Guidelines for antipsychotic use in first episode psychosis recommend that medication be chosen initially on the basis of side-effect profile with some excluding olanzapine. Doses at the lower end of the range should be used. This study assess the influence of guidelines on clinical practice.

Methods

A retrospective examination of prescribing practices was conducted for 465 first episode psychosis patients, of whom 146 were assessed as part of an epidemiologic study (1995-1999) and 319 were treated at a specialist early intervention for psychosis (EIP) service (2005-2016). Treatment with antipsychotic medication did not exceed 30 days at study entry.

Results

First generation antipsychotics were prescribed for 65% of the early cohort compared with 4.3% of the EIP cohort. Olanzapine was initially prescribed for 79.7% of EIP patients. Guidelines did not appear to influence the choice of antipsychotic medication. Initial doses of medication were frequently low in both cohorts (71% and 78.6%). In the EIP service, initial doses were higher among younger patients (p=0.048) and inpatients (p=0.031). Meanwhile, lower Global Assessment of Function scores at baseline (p=0.002), greater positive symptom scores (p=0.004) and treatment in the inpatient setting (p=0.035) all predicted dose increases after one month with the EIP service.

Conclusion

Second generation antipsychotic prescribing predominates, but guidelines are often overlooked when choosing olanzapine notwithstanding lower initial dosages. EIP services should include proactive support for optimising medicines in line with evidence-based guidelines.

STRENGTHS AND LIMITATIONS OF THE STUDY

- This 21 year study examines changes in antipsychotic prescribing practices for a naturalistic cohort of first-episode psychosis patients during two discrete periods before and after the introduction of an early intervention for psychosis service.
- All 465 patients had an objectively-rated diagnosis of first-episode psychosis using validated instruments.
- All participants had little or no antipsychotic exposure before the study.
- A limitation of the study is its retrospective nature, meaning some data were missing.
- Rates of adherence to international prescribing guidelines may be reflect the fact that they were not specifically promoted in this study setting.

INTRODUCTION

Early intervention for psychosis (EIP) has been shown to ameliorate illness severity, reduce hospitalisation and improve aspects of social functioning such as involvement in school or work.[1] Benefits are sustained in the short to medium term.[2 3] The components of an EIP service differ with regard to the specific interventions offered. Common themes, however, include use of medication, psychosocial interventions such as cognitive behavioural therapy (CBT), family interventions, rehabilitative interventions and psychoeducation.[1] EIP models of care also vary with some services delivered by specialist stand-alone multidisciplinary teams and others by enhanced community mental health teams (CMHT) whereby staff within CMHTs care for people with EIP in addition to their usual roles. 'Hub and spoke' models involve a centralised specialist 'hub' which supports specialist staff or 'spokes' embedded in local CMHTs.[4] Despite the variations in how the EIP services are delivered, recent evidence suggests that the early intervention approach is likely to be cost-effective.[5 6]

Antipsychotic medications are a key component of care for those experiencing psychosis. Response to a first antipsychotic medication in first episode psychosis (FEP) is high with up to 80% achieving a reduction in symptoms.[7] Maintenance treatment with antipsychotic medications reduces hospitalisations, improves life expectancy and enhances functional outcomes.[8-11] Given the evidence that no one agent has shown significant superiority in terms of efficacy in this population [12], international guidelines recommend that tolerability should be the main influence when it comes to the choice of medication.[13] Furthermore, doses of medication should also be lower in FEP than those used to treat later episodes of schizophrenia because people experiencing FEP are particularly sensitive to the effects and to the side effects of antipsychotic medication.

Pharmacological treatment guidelines have evolved over the lifetime of early intervention services with a notable change being the role of second generation antipsychotics (SGA). [14-16] The National Institute for Health and Care Excellence (NICE), for example, recommended SGAs as initial treatment in the early 2000's. Emerging evidence regarding the relative risks of SGAs, particularly metabolic risks, led to a change in the 2009 update of the NICE guidelines with initial choice being driven by side effect profile rather than classification of antipsychotics.[16] The Patient Outcome Research Team (PORT) guidelines, also updated in

2009, specifically excluded olanzapine as a first line treatment option [15] and other guideline development groups have followed suit.[14 17] EIP services vary in their approach to medication with limited published information on prescriber training, treatment goals, algorithms or guidelines and delivery of treatment.[18] This is perhaps surprising given the evidence of sub-optimal use of antipsychotic medication in clinical practice.[19 20]

In this study we describe the pattern of antipsychotic medication use in two cohorts of FEP patients before and after the introduction of an EIP service in the context of evolving clinical practice guidelines. Our objectives were to determine (i) the effect of international guideline recommendations on the initial choice and dose of antipsychotic medication (ii) whether clinical or demographic factors at baseline influenced the choice of medication or the initial dose of medication for patients supported by an EIP service.

METHODS

Study Design

The study is a retrospective examination of the medication prescribed for two cohorts of FEP patients before and after the introduction of EIP services. Data were gathered from clinical records, the EIP study database and electronic prescribing records. This article was written using the STROBE guidelines for reporting cohort studies.[21]

Study Setting

Data were extracted from a community based mental health service located in an urban area of south county Dublin with a current population of approximately 187,000. A large private hospital, located within the catchment area also participated in the study. EIP services were preceded by an epidemiological First Episode Study (FES) between 1995 and 1999.[22] Evidence from this study was used to secure funding for the Dublin and East Treatment and Early Care Team (DETECT). The specialist DETECT team offers rapid assessment leading to phase specific psychological and family interventions. Antipsychotic medication use is managed by the patient's usual psychiatrist.

Participants and Inclusion Criteria

The FES cohort (C 1) was an epidemiologically complete sample recruiting all patients presenting in the catchment area with a first lifetime episode of psychosis between 1995 and 1999. Patients were included if they were aged 12 or over and had received less than 30 days antipsychotic treatment. Cases included in the DETECT cohort (C 2) were assessed by the EIP service between 2005 and 2016 and gave consent to participate in the study. Participants were aged between 16 and 65 and had received less than 30 days antipsychotic treatment before the EIP service assessment. The cohorts are described in Figure 1.

Assessments

Participants were included if they had a diagnosis of FEP based on the Structured Clinical Interview (SCID) for DSM-IV axis I disorders.[23] The Global Assessment of Functioning Scale (GAF) was used was used to rate subjectively social, occupational and psychological function. Scores range from 100 (extremely high functioning) to 1 (severe impairment).[24] For Cohort 1, psychological symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS).[25] The PANSS is scored by summation of individual items to produce positive symptom and negative symptom domain scores in a range of 7-49 and a composite general psychopathology score in the range of 16 to 112. The Scale for Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS), well established rating scales used in clinical research, were used to assess symptoms in C2.[26] SANS measures negative symptoms on a 25 item, 6-point scale. Items are listed under the five domains of affective blunting, alogia, avolition/apathy, anhedonia/asociality, and attention. SAPS measures positive symptoms on a 34 item, 6-point scale. Items are listed under hallucinations, delusions, bizarre behaviour, and positive formal thought disorder. All scales were administered by trained clinicians who participated with inter-rater reliability. Duration of untreated psychosis (DUP) was defined as the interval between first experience of psychotic symptom(s) and presentation to the psychiatric services for initiation of treatment; first manic symptom(s) were used for bipolar disorder.[27]

Antipsychotic Prescribing Data

Prescribing data pertaining to C1 were compiled from paper charts. For the EIP cohort (C2), prescribing data at the time of clinical assessment (T1) was collected as part of a larger study of outcomes in first episode psychosis following the introduction of an EIP service. Medication at the time of initial assessment was recorded in the study database by the clinician carrying out the assessment. Data missing from the database and prescribing information following one month of engagement with the services (T2) were collected using hospital dispensing records and outpatient electronic prescribing records. Business intelligence was used to extract the relevant prescribing data from the electronic patient records. It was taken that prescriptions generated within one week of the specified time points were the current medications. Cases for which no medication data were available were excluded.

Regular antipsychotic medication were included. Antipsychotics used for short periods on a 'pro re nata' (PRN) basis or for rapid tranquilisation were excluded. Where medications were being switched, we considered this to be appropriate polypharmacy and included the new antipsychotic as the choice assuming that the switch would be completed. Doses of antipsychotic medication were categorised into 'low', $\leq$ 50% of the current British National Formulary (BNF) maximum dose; medium, $\geq$51% to $\leq$100% of current BNF maximum dose; and 'high' dose >100% of current BNF maximum dose. An exception to this was risperidone for which 6mg was considered the maximum dose in FEP. The current BNF dosing standards for haloperidol were applied and it should be noted that the BNF maximum dose has reduced over the lifetime of this study.

Statistical Methods

Initially, descriptive statistics were used to describe baseline characteristics and general prescribing patterns in both cohorts. Means and standard deviations are reported for continuous variables and frequencies and percentages for categorical variables. For continuous scales which show evidence of or are expected to show some skew, a median and interquartile range (IQR) is also presented. Scatterplots were used to display trends in olanzapine prescribing over time and an indicator included at 2009 when guidelines were first published advising against the use of olanzapine as an initial medication in FEP.

Demographics of those starting on olanzapine, compared to those starting on an alternate were explored. Furthermore, patient characteristics of those initiated on a low dose, versus those initiated on a medium/high dose were explored. Characteristics of those requiring a change in dose one month after engagement with the EIP service (dose increase/decrease) were also explored. For categorical variables a chi-squared test was used and for continuous variables, a Mann-Whitney test was used. Statistical analysis was conducted using SPSS version 24.

Ethics

Ethics approval was granted by the local research ethics committee.

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical baseline data from the FES (C1) are described in Table 1 and have previously been reported.[27] This was an epidemiologically complete sample of all people presenting with FEP. Demographic and clinical characteristics for the EIP service (C2) were included for those who consented to participate in the study and for whom prescribing data were available (Table 1). Participants were predominantly male with an average age of 32.5 years. Most were assessed in the inpatient setting (67.7%) and schizophrenia spectrum was the most common initial diagnosis (39.2%).

Table 1. Baseline description of demographic and clinical characteristics of two cohorts of patients presenting between 1995 and 2016 for assessment of first episode psychosis prior to (C1) and after (C2) the introduction of an EIP service

	C 1 (1995 to 1999) N = 171			**C 2 (2005 to 2016) N = 319**
Gender	N (%)			N (%)
Male	99 (58)			189 (59.2)
Female	72 (42)			130 (40.8)
Age	Mean (SD)			Mean (SD)
	28.5 (11.1)			32.5 (11.3)
	N (%)			N (%)
Inpatient on assessment (%)	144 (84.2)			216 (67.7)
Initial Diagnosis[a]				
Schizophrenia Spectrum	101 (59.1)			124 (39.2)
Substance Induced Psychosis	12 (7)			45 (14.2)
Major Depressive Disorder	11 (6.4)			36 (11.4)
Bipolar Disorder	25 (14.6)			35 (11.1)
Delusional Disorder	13 (7.6)			35 (11.1)
Brief Psychotic Disorder	0			22 (7)
All other psychotic diagnoses	4 (5.2)			19 (6)
	Mean	Median	Range	Median (IQR)
DUP (months)[b]	17.9	5	0.25-240	3 (0.63 – 13)
GAF[c]	22.9			35 (30 - 48.5)
PANSS- Total [d]	74.4			
PANSS- Negative [e]	15.7			
PANSS- Positive [f]	21.3			
SAPS- Total [g]				18 (10-31)
SANS- Total [h]				12 (3-22)

IQR= Interquartile range; SD= Standard deviation

[a] 3 missing C2

[b] DUP= Estimated Duration of Untreated Psychosis. 5 missing C1; 156 missing C2

[c] GAF = Global Assessment of Functioning. 6 missing C2

[d] PANSS= Positive and Negative Symptom Scale Total Symptom Score

[e] PANSS- Negative = PANSS negative symptom score

[f] PANSS-Positive = PANSS positive symptom score

[g] SAPS- Total = Scale for Assessment of Positive Symptoms total score. 11 missing C2

[h] SANS- Total = Scale for Assessment of Negative Symptoms total score. 14 missing C2

Choice of Antipsychotic Medication

Prescribing data for a total of 465 patients were included, 146 in C1 and 319 in C2. Cases were excluded if prescribing data was not available for C1 (n=25) or if there was no prescribing data at time of initial assessment or one month follow up for C2. Prescribing patterns of antipsychotic medications are described in Table 2. The proportion of SGAs increased from 32.2% in C 1 to over 90% in C 2. FGA use predominated in C1 (65.1%), of which the most frequently chosen was sulpiride (19.2%), followed by thioridazine (11%) and haloperidol (10.3%). Olanzapine was the most frequently prescribed SGA throughout the time of the study and the prescribing frequency increased per year as represented in Figure 2. Guidelines published in 2009 advising against the use of olanzapine as an initial medication in FEP and widening the choice to first or second generation medicines did not appear to have an impact on prescribing patterns. Table 3 describes the demographic data of those not prescribed olanzapine at initial assessment by the EIP service (C2).

Table 2. Antipsychotic prescribing patterns among two cohorts of patients presenting for assessment of first episode psychosis before and after the introduction of an early intervention for psychosis service

	Cohort 1	**Cohort 2**	
	n=146	T1 (n=305)	T2 (n=293)
	N (%)	N (%)	N (%)
Second Generation			
Olanzapine	36 (24.7)	243 (79.7)	210 (71.7)
Risperidone (oral)	8 (5.5)	25 (8.2)	22 (7.5)
Amisulpride	2 (1.4)	7 (2.3)	11 (3.3)
Quetiapine	1 (0.7)	6 (2.0)	9 (2.7)
Aripiprazole		1 (0.3)	4 (1.4)
Risperidone LAI			3 (0.9)
Paliperidone (oral)			1 (0.3)
Paliperidone LAI			5 (1.5)
Second Generation Total	**47 (32.2)**	**282 (92.4)**	**265 (90.4)**
First Generation			
Sulpiride	28 (19.2)	1 (0.3)	1 (0.3)
Thioridazine	16 (11)	4 (1.3)	
Haloperidol	15 (10.3)		4 (1.4)
Chlorpromazine	13 (8.9)	3 (1)	1 (0.3)
Trifluoperazine	9 (6.2)	2 (0.7)	2 (0.6)
Flupenthixol Depot	4 (2.7)		1 (0.3)
Pimozide	4 (2.7)		1 (0.3)
Zuclopenthixol depot	1 (0.7)		5 (1.5)
Zuclopenthixol oral	1 (0.7)	1 (0.3)	
Flupenthixol (oral)	1 (0.7)	2 (0.7)	1 (0.4)
Fluphenazine	1 (0.7)		
Pipotiazine	1 (0.7)		
Perphenazine	1 (0.7)		
First Generation Total	**95 (65.1)**	**13 (4.3)**	**16 (5.5)**
No antipsychotic	4 (2.7)	10 (3.3)	12 (3.6)
T1 = Time of initial assessment T2 = One month following initial assessment LAI = Long acting injection			

Table 3. Baseline demographic and clinical characteristics of patients presenting for assessment of first episode psychosis who were commenced on antipsychotic medication other than olanzapine

	Patients not prescribed olanzapine at time of initial assessment N = 52
Gender	N (%)
Male	29 (55.8)
Female	23 (44.2)
	Mean (SD)
Age	30.1 (9.7)
	N (%)
Inpatient on assessment	33 (63.5)
Initial Diagnosis[a]	
Schizophrenia Spectrum	24 (47.1)
Substance Induced Psychosis	1 (1.9)
Major Depressive Disorder	1 (1.9)
Bipolar Disorder	8 (15.7)
Delusional Disorder	8 (15.4)
Brief Psychotic Disorder	2 (3.8)
All other psychotic diagnoses	7 (13.5)
	Median (IQR)
DUP (months)[b]	5 (1-14)
GAF[c]	37 (30 – 52)
SAPS- Total[d]	15 (10 – 28)
SANS- Total[e]	13 (4.5 – 22.5)
SD = Standard Deviation; IQR = Interquartile range [a] DUP= Estimated Duration of Untreated Psychosis. 1 missing [b] GAF = Global Assessment of Functioning. 20 missing [c] SAPS- Total = Scale for Assessment of Positive Symptoms total score 1 missing [d] SANS- Total = Scale for Assessment of Negative Symptoms total score. 3 missing	

Data were available for C2 showing that 10 (3.3%) patients at T1 and 11 (3.9%) patients at T2 were not prescribed antipsychotic medications. At initial assessment those who did not receive an antipsychotic medication had the following initial diagnoses: 'All other psychotic diagnosis' (n=4), substance induced psychosis, major depressive disorder (n=2), brief psychotic episode (n=2) and delusional disorder. However, this data was only identifiable for patients who received prescriptions for other medication on the electronic database and may be an underestimate.

Five patients were prescribed long acting injection or depot formulation of antipsychotic medication in C1. While no patient was initiated on LAI at initial presentation for C2, 14 (4.8%) had commenced an LAI by one month of treatment. Of the 319 cases in C2, data on both the medication used at initial assessment and at one month are available for 280 cases. Of these 35 (12.5%) patients required a switch of antipsychotic medication within one month. The demographic profile of the patients who required a switch in medication or formulation is described in Table 4 and the choice of medication or formulation is described in Table 5.

Table 4. Baseline demographic and clinical characteristics of patients presenting for assessment of first episode psychosis who required a switch in antipsychotic medication or formulation during the first month of engagement with an EIP service

	Patients requiring a switch in antipsychotic medication or formulation over the first month N=35
Gender	*N (%)*
Male	21 (60)
Female	14 (40)
	Mean (SD)
Age	35 (10.3)
	N (%)
Inpatient on assessment	30 (85.7)
Initial Diagnosis[a]	
Schizophrenia Spectrum	14 (40)
Substance Induced Psychosis	2 (5.7)
Major Depressive Disorder	4 (11.4)
Bipolar Disorder	5 (14.3)
Delusional Disorder	5 (14.3)
Brief Psychotic Disorder	4 (11.4)
All other psychotic diagnoses	2 (5.7)
	Median (IQR)
DUP (months)[b]	6 (0.5 – 22)
GAF[c]	31 (30 – 47)
SAPS- Total[d]	22 (12.75 – 34)
SANS- Total[e]	15 (3 – 25.25)

SD = Standard Deviation; IQR = Interquartile range
[a] DUP= Estimated Duration of Untreated Psychosis.
[b] GAF = Global Assessment of Functioning. 18 missing.
[c] SAPS- Total = Scale for Assessment of Positive Symptoms total score. 3 missing.
[d] SANS- Total = Scale for Assessment of Negative Symptoms total score. 3 missing.

Table 5. Pattern of medication changes between initial assessment at an early intervention for psychosis service (T1) and following one month of engagement with the service (T2).

T1	T2	N (%)
Olanzapine	Risperidone	6 (17.1)
Olanzapine	Amisulpride	4 (11.4)
Olanzapine	Quetiapine	3 (8.6)
Olanzapine	Zuclopenthixol depot	3 (8.6)
Risperidone	Risperidone LAI	3 (8.6)
Olanzapine	Aripiprazole	2 (5.7)
Olanzapine	Paliperidone LAI	2 (5.7)
Olanzapine	Risperidone LAI	1 (2.9)
Olanzapine	Haloperidol	1 (2.9)
Olanzapine	Haloperidol Depot	1 (2.9)
Olanzapine	Paliperidone	1 (2.9)
Olanzapine	Pimozide	1 (2.9)
Olanzapine	No medication	1 (2.9)
Risperidone	Olanzapine	1 (2.9)
Risperidone	Paliperidone LAI	1 (2.9)
Chlorpromazine	Amisulpride	1 (2.9)
Flupenthixol	Flupenthixol depot	1(2.9)
Chlorpromazine	Amisulpiride	1(2.9)
Haloperidol	Olanzapine	1(2.9)

Dose of Antipsychotic Medication

Doses of medication at initial assessment were generally categorised as low in both cohorts (C1, 71% and C2, 78.6%). Table 6 summarises patient characteristics by low or medium to high doses of antipsychotic medication at initial assessment for C2. There is evidence that age was statistically significantly lower in those commenced on a medium to high dose of medication compared with a low initial dose of medication ($p = 0.048$). Furthermore, inpatient care was statistically significantly associated with the initiation of antipsychotic medication at medium to high doses ($p= 0.031$).

Table 6. Patient characteristics summarised by low or medium to high dose of antipsychotic medication at initial assessment for patients engaged in an early intervention for psychosis service (C2)

	Low dose (n=228)	**Medium/high dose** (n=52)	**p-value**[a]
Age, mean (SD)	33.5 (11.3)	30.6 (11.4)	**0.048**
Sex, n (%)			
Male	133 (58.3)	33 (63.5)	0.461
Female	95 (41.7)	19 (36.5)	
Diagnostic category, n (%)			
Schizophreniform psychosis	134 (63.5)	27 (52.9)	0.14
Affective psychosis	50 (23.7)	12 (23.5)	
Substance misuse and organic	27 (12.8)	12 (23.5)	
Treatment setting			
Inpatient, n (%)	151 (66.2)	43 (82.7)	**0.031**
Outpatient, n (%)	77 (33.8)	9 (17.3)	
GAF, median (IQR)	35 (30.0 – 49.0) n= 224	35 (30.0 – 40.5) n= 52	0.977
DUP (months), median (IQR)	3 (1.0 – 20.0) n=127	3 (0.5 – 7.0) n=27	0.212
SAPS Total score, median (IQR)	18 (10.0 – 30.0) n=221	24 (13.0-35.0) n=49	0.096
SAPS excitatory/agitation score			
Symptoms present[b], n (%)	82 (36.4)	17 (34.0)	0.745
Symptoms not present[c], n (%)	143 (63.6)	33 (66.0)	

[a]Mann-Whitney test or chi-squared test as appropriate
IQR = Interquartile Range
DUP= Estimated Duration of Untreated Psychosis
GAF = Global Assessment of Functioning
SAPS- Total = Scale for Assessment of Positive Symptoms total score
[b]Score of 0 = none or 1= questionable on the SAPS excitatory/agitation score
[c]Score of 2=mild, 3=moderate, 4= marked or 5= severe on the SAPS excitatory/agitation score

After one month of treatment the proportion of people in C2 requiring medium or high doses of medication increased from 17.9% to 42.7%. Of these, 4 patients (1.2%) were treated with doses above the BNF maximum, all of which were olanzapine at doses of 22.5 to 30mg per day.

Data on the dose of medication at both time points was available for 268 patients. Of these, 72 (26.8%) required an increase in dose over the first month of engagement with the early intervention service (Table 7). All of those who required an increase in dose had received an initial low dose of medication which was increased to a medium dose for 71 patients and a high dose for 1 patient. The dose of medication decreased for 10 (3.7%) people between initial assessment and following one month of engagement with the service. All 10 had been started on a medium dose of antipsychotic and the dose was reduced to a low dose over the first month. Medication was discontinued for one person who initially started on a low dose of medication. The dose for 186 people (69.4%) remained unchanged over the first month of engagement with the EIP service.

Table 7. Patient characteristics summarised by dose increase or dose decreased/unchanged following one month of engagement with an early intervention for psychosis service (C2)

	Dose increased (n=72)	**Dose unchanged or decreased** (n=196)	**p-value[a]**
Age, mean (SD)	30.4 (10.5)	32.9 (11.5)	0.134
Sex, n (%)			0.527
Male	46 (63.9)	115 (58.7)	
Female	26 (36.1)	81 (41.3)	
Diagnostic category, n (%)			
Schizophreniform psychosis	40 (58)	114 (63.7)	0.681
Affective psychosis	17 (24.6)	40 (22.3)	
Substance misuse and organic	12 (17.4)	25 (14)	
Treatment setting			**0.035**
Inpatient, n (%)	58 (80.6)	130 (66.3)	
Outpatient, n (%)	14 (19.4)	66 (33.7)	
GAF, median (IQR)	30 (25.3-40.0) n=72	39 (30.0 – 50.0) n= 191	**0.002**
DUP (months), median (IQR)	3 (0-20) n=33	4.25 (1.0-16.5) n=114	0.212
SAPS Total score , median (IQR)	24 (12.0-35.0) n=71	17 (10.0-28.0) n=188	**0.004**
SAPS excitatory/agitation score (n=263)			
Symptoms present[b]	31 (43.7%)	61 (31.8%)	0.099
Symptoms not present[c]	40 (56.3%)	131 (68.2%)	

[a]Mann-Whitney test or chi-squared test as appropriate
IQR = Interquartile Range
DUP= Estimated Duration of Untreated Psychosis
GAF = Global Assessment of Functioning
SAPS- Total = Scale for Assessment of Positive Symptoms total score
[b]Score of 0= none or 1= questionable on the SAPS excitatory/agitation score
[c]Score of 2=mild, 3=moderate, 4= marked or 5= severe on the SAPS excitatory/agitation score

Patient characteristics by dose increase or by dose remaining unchanged or decreased can be seen in Table 7. Dose increases were statistically significantly associated with the inpatient treatment setting (p= 0.035). There is also statistically significant evidence of an association between poorer functioning at assessment (indicated by a lower score on the GAF) and the requirement to increase the dose of medication over the first month (p = 0.02). Dose increases were also statistically significantly associated with greater positive symptom scores on the SAPS (p=0.004) but not with the presence of excitatory/agitation symptoms (p=0.099).

DISCUSSION

Summary of Findings

This study describes the pattern of antipsychotic prescribing for a naturalistic cohort of patients presenting for assessment of FEP in a geographically defined catchment area prior to and following the introduction of an EIP service. The data demonstrates the changes over time in the choice of antipsychotic medication, the move towards predominantly second generation antipsychotic use and the prevalence of olanzapine as a first choice medication. Guidelines issued in both Europe and America widening the choice of antipsychotic medication or specifically not recommending olanzapine as an initial choice of agent, do not appear to have had an impact on prescribing patterns. Additional indicators of good practice, such as the use of low doses of antipsychotic medication for the initial treatment of FEP and the avoidance of high doses and antipsychotic polypharmacy are demonstrated. We did not find any patient-related demographic or clinical factors that predicted the initial choice of antipsychotic medication. Younger age and inpatient treatment setting were associated with a higher initial dose of antipsychotic medication (>50% BNF maximum). Increasing dose requirements over the first month of engagement with an EIP service were associated with poorer global functioning at baseline, greater positive symptoms at baseline and the inpatient treatment setting.

Comparison with Previous Literature

While the prevalence of use of olanzapine is very high in our study by comparison, the preference for olanzapine as a first choice antipsychotic has been previously been reported in the literature.[28-31] Spanish prescribing practices for FEP were described in a naturalistic prospective study by Bioque *et al*.[30] Patients were included if they were between 7 and 35 years presenting to a FEP service across 16 centres over a 3 year period with not greater than 12 months previous antipsychotic exposure. Of the 335 patients, 22.7% were prescribed olanzapine, 22% risperidone and 9.6% aripiprazole.

Tungazara *et al* reported antipsychotic prescribing patterns across EIP services in the UK with a rate of 35% reported for olanzapine as the most common first choice antipsychotic.[31] Clarke *et al* retrospectively identified 66 patients presenting with FEP in a Dublin catchment

area through clinician recall of cases. A prescribing rate of 58% for olanzapine was reported although, given the methodology of case identification, it is possible that this may not be a complete picture of prescribing practice.

In the Recovery After an Initial Schizophrenia Episode- Early Treatment Programme (RAISE-ETP) study, Robinson *et al* found that, at the point of engagement with an EIP service, medication review would be beneficial for 39.4% of the 404 patients enrolled in the study. The reasons for medication review included the use of olanzapine (31.2%) and the use of high dose regimens (8.8%) or combinations of antipsychotic medications (23.3%).[32] Notably, 44.9% of olanzapine prescriptions were for doses higher than those recommended in the PORT guidelines for FEP in comparison to 7.8% of risperidone prescriptions. Prescription of FGA's was more common for uninsured patients. In our study, cost is unlikely to have been a factor in prescribing decisions because of the system of medication reimbursement. RAISE-ETP enrolled participants who were aged between 15 and 40, with a diagnosis of schizophreniform disorder or brief psychotic episode and a maximum cumulative use of 6 months of antipsychotic treatment. The median exposure to antipsychotic medication at the time of assessment was 2.2 months.

Guidelines recommend commencing antipsychotic medication at the lower half of the dose range in FEP.[15 16] We therefore took a pragmatic approach to describing the pattern of antipsychotic doses by expressing dose as a percentage of the BNF maximum. Guideline recommendations were generally adhered to with 78.6% of patients prescribed lower doses at initial presentation and the use of high dose medication regimens was negligible at both initial assessment and after one month of treatment. Bioque *et al* reported that 8.9% of patients received higher doses of medication, by comparison.[30] Our description of antipsychotic use in the very early stages of treatment for FEP may explain the low rates of antipsychotic polypharmacy and high dose treatment strategies in comparison to other studies.[30 32]

Clinical Implications

A positive first experience of using antipsychotic medicines is likely to have an impact on future engagement with services and outcomes.[33 34] Careful consideration of the first antipsychotic medication involves balancing side effects with expected benefits and

incorporating the patient perspective through a shared decision making approach. Managing side effects, however, is a significant challenge with the risks of metabolic abnormalities, sexual problems and movement disorders among the many potential disadvantages of using these medications. A network meta-analysis by Zhu *et al* incorporating 19 trials involving 2669 patients found little to differentiate between SGAs in terms of efficacy for FES.[12] Their conclusion that the choice of treatment in FES should be guided primarily by side effects reflects the recommendations of previously published guidelines.[13]

Olanzapine has a higher risk of inducing weight gain and metabolic abnormalities in comparison to all of the other antipsychotics that could potentially be used as an initial treatment option in FEP.[35 36] Antipsychotic induced weight gain causes considerable patient distress, has serious general health implications and leads to early discontinuation of medication.[37] While a reduction in the proportion of FEP patients using olanzapine as an initial treatment could be beneficial, should olanzapine continue to be used as a first line agent then strategies to prevent and manage weight gain should form part of an EIP programme. Lifestyle interventions [38], metformin [39] or liraglutide [40] are potential options.

Clinical practice guidelines in psychiatry are often difficult to implement.[20 41] However proactive support for prescribing practice can be an effective means of improving the quality of medication use in a first episode service.[18 42 43] Observational studies by Yoshimura *et al* and Yeisen *et al* demonstrated that the initial choice of antipsychotic can be influenced by locally implemented algorithms.[42 43] Robinson *et al* developed the NAVIGATE prescribing principals and the COMPASS decision making tool which was designed to facilitate communication between the patient and the prescriber in the RAISE trial.[18] Training was provided for prescribers and they were given ongoing support throughout the study. Over a 2 year period study participants (n=223) had more medication visits, were more likely to use a medication that conformed to the NAVIGATE guidelines, experienced fewer side effects and gained less weight than those who has received usual community care (n=181). Adherence estimator scores also improved in the NAGIGATE group but not in the community group. The models of care for EIS internationally give varying attention to supporting medicines optimisation.[1] This evidence and the results of our study suggest that EIP services could benefit from proactive support for prescribing practice.

The role of long acting injection formulations (LAI) for those experiencing FEP is currently the focus of much debate. Although not recommended as first line agents in guidelines [13] unless the patient expresses a preference for this formulation, leading clinicians are beginning to advocate for their use at an earlier stage and perhaps to be offered as an initial treatment.[44] The advantages may be reduced hospitalisation, more stable therapeutic blood levels with no additional side effect burden and convenience for the patient.[45] Confirming adherence through the use of LAIs may lead to better treatment decisions and earlier recognition of treatment resistance. However, barriers to the use of these formulations include reluctance on the part of patients to engage in their use and a view that there may be a coercive nature to injecting medication.[46] In this study the prevalence of LAI use is low, with some historical use of the FGA's described in our first cohort. The preference for SGA's may have had an impact on the use of LAI's until the development of the first second generation LAI formulation of risperidone.

Strengths, Limitations and Future Research

We report prescribing data from a naturalistic cohort with inclusion criteria reflecting the age range and diagnoses presenting to an EIP service. The longitudinal data allows a view of the pattern of prescribing practice over a 20 year period before and after the introduction of specialist EIP service. We were also able to describe the clinical use of the medications in terms of dose changes and need to switch medication or formulation over the first month of engagement with the EIP service. In studies regarding antipsychotic use in an FEP population, patients were often treated with antipsychotic medication for a number of months before assessment by an EIP service and therefore may not accurately reflect the first choice of antipsychotic or initial dose.[28 30-32] In our study, participants had less than three weeks antipsychotic exposure.

It is possible that patient related factors other than those assessed, such as sociodemographic factors or clinical metabolic parameters, may have had an influence on the choice or dose of antipsychotic medication. The retrospective nature of this study led to some missing data in both cohorts. The pattern of prescribing in the interim period between the FES and the EIP studies could not be described. International prescribing guidelines are not specifically promoted in Ireland and there are no local guidelines for FEP in the Irish

mental health services. Their influence may, therefore, be expected to be poor. It would be useful to examine the topic prospectively to include shared decision making processes and clinician related factors and investigate the impact on patient outcomes. Future local or national guidelines may influence prescribing practice and include decision support tools and proactive management protocols to mitigate the potential side effects of antipsychotic medication.

CONCLUSION

There is clearly a move toward the use of SGAs as initial treatment for FEP. Guidelines which recommend avoiding olanzapine as an initial choice based on its side effect profile, do not appear to have had an influence on prescribing practice. Antipsychotics are generally initiated at low doses. Age, symptoms, functioning and inpatient status may all play a role in determining medication doses. Given the importance of early experiences with medication consideration should be given to including a proactive approach to medicines optimisation within the EIP model of care. This could include locally agreed guidelines, decision support tools for both patients and clinicians and active management of side effects.

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CONTRIBUTIONS

DK designed and conducted the study in collaboration with JS and MC. DK extracted the data for the DETECT cohort from the DETECT research database and hospital prescribing records. RD and CB extracted the data in relation to the first episode study. DK analysed the data with advice from FB. DK wrote the manuscript with input from SMcW, FB, JS and MC.

COMPETING INTERESTS

The authors report no competing interests

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DATA SHARING STATEMENT

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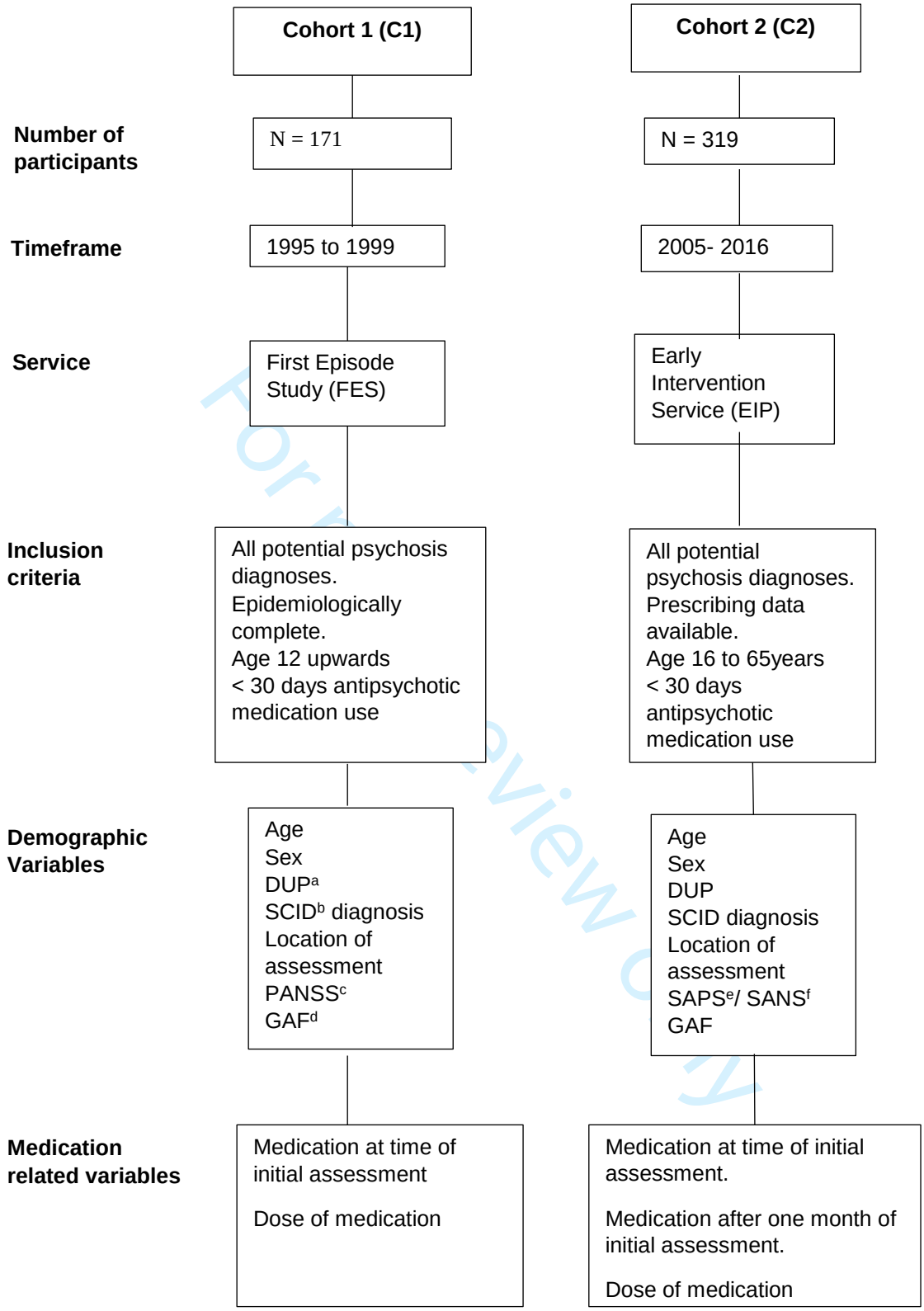

Figure 1. Description of cohorts of patients presenting to an early intervention service, timeframe of presentation, inclusion criteria, demographic and medication related variables

[a]Duration of Untreated Psychosis; [b]Structured Clinical Interview for Diagnosis; [c]Positive and Negative Symptom Scale; [d]Global Assessment of Functioning; [e]Scale for Assessment of Positive Symptoms; [f]Scale for Assessment of Negative Symptoms

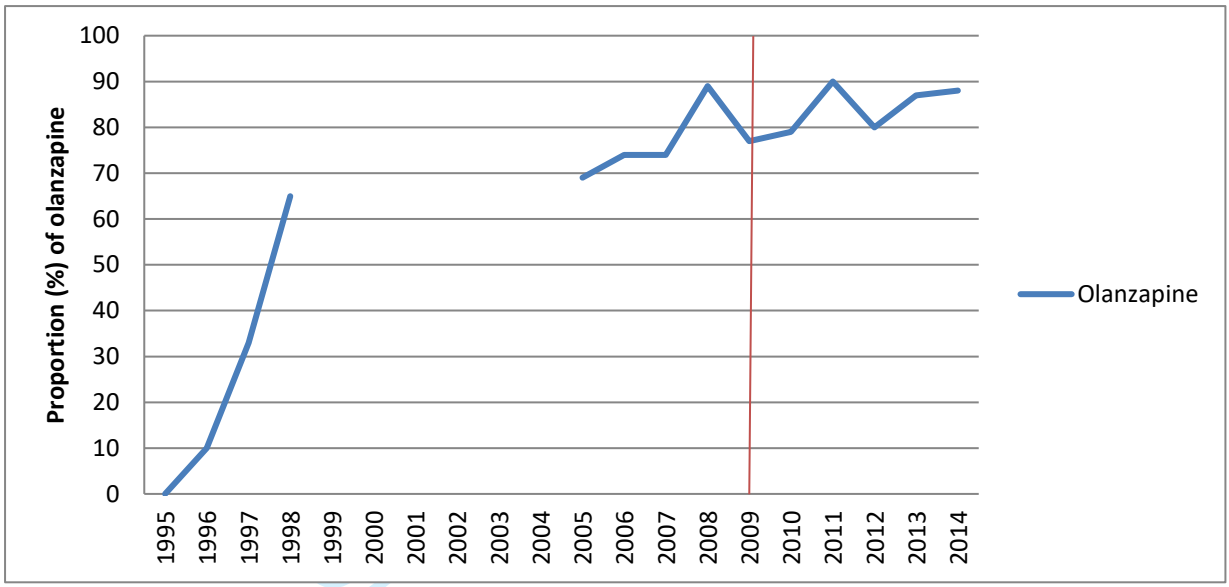

Figure 2 Proportion of olanzapine (%) prescribed per year for patients presenting for assessment of first episode psychosis

Guidelines published in 2009 advising against the use of olanzapine as an initial medication in FEP and widening the choice to first or second generation antipsychotics (orange line).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8,9
		(b) Give reasons for non-participation at each stage	8,9
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	10,11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-17
		(*b*) Report category boundaries when continuous variables were categorized	10-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prescribing Pattern of Antipsychotic Medication for First Episode Psychosis: A Retrospective Cohort Study

Dolores Keating PhD[1,2], Stephen McWilliams MD[3,4], Fiona Boland PhD[5], Roisin Doyle MSc[6], Caragh Behan PhD[7], Judith Strawbridge PhD[2] and Mary Clarke MD [4,6]

Corresponding author:

Dr Dolores Keating, [1]Pharmacy Department, Saint John of God Hospital, Stillorgan, Co Dublin, Ireland;

[2]School of Pharmacy, Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin 2.

Tel +35312771607. Email Dolores.keating@sjog.ie

Co-authors

Dr Stephen McWilliams, [3]Saint John of God Hospital, Stillorgan, Co Dublin, Ireland

[4]School of Medicine, University College Dublin, Dublin 4.

Dr. Fiona Boland, [5]Data Science centre and HRB Centre for Primary Care Research, Royal College of Surgeons in Ireland, 123 St Stephens Green, Dublin 2, Ireland

Roisin Doyle, [6]DETECT Early Intervention in Psychosis Service, Blackrock, Co Dublin, Ireland

Dr Caragh Behan, [7]Cluain Mhuire Services, Newtownpark Avenue, Blackrock, Co Dublin

Prof Judith Strawbridge, [2]School of Pharmacy, Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin 2.

Prof Mary Clarke, [6]DETECT Early Intervention in Psychosis Service, Blackrock, Co Dublin, Ireland

[4]School of Medicine, University College Dublin, Dublin 4.

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ABSTRACT

Objective

Guidelines for antipsychotic use in first-episode psychosis (FEP) recommend that medication be chosen initially on the basis of side-effect profile with doses at the lower end of the range. Our objective was to describe the pattern of antipsychotic use in FEP over a period of 21 years in the context of changing clinical guidelines and the development of specialist Early Intervention for Psychosis (EIP) services.

Setting

A community-based mental health service in south County Dublin (population 187,000) and a large private hospital.

Participants

Participants included 465 FEP patients [146 from an epidemiological study (1995-1999) and 319 from a specialist early intervention for psychosis (EIP) service (2005-2016). Treatment with antipsychotic medication did not exceed 30 days at study entry.

Outcome Measures

This is a descriptive study of prescribing practices in the context of service development and changing guidelines.

Results

First-generation antipsychotics were prescribed for 65% of the early cohort compared with 4.3% of the EIP cohort. Olanzapine was initially prescribed for 79.7% of EIP patients. Initial doses of medication were frequently low (≤ 50% BNF maximum) in both cohorts (71% and 78.6%). The demographic and clinical factors investigated did not influence the initial choice of antipsychotic medication significantly. Univariate logistic regression analysis suggested inpatient treatment setting was associated with a higher initial dose (>50% BNF maximum) of antipsychotic medication. Increasing dose requirements over the first month of engagement with an EIP service was associated with poorer global functioning at baseline, greater positive symptoms at baseline and the inpatient treatment setting. However, these associations were not seen in the multivariable model.

Conclusions

Second-generation antipsychotic prescribing predominates, but guidelines are often overlooked when choosing olanzapine notwithstanding lower initial dosages. EIP services should include proactive support for optimising medicines in line with evidence-based guidelines.

STRENGTHS AND LIMITATIONS OF THE STUDY

- This 21 year study describes antipsychotic prescribing practices for a naturalistic cohort of first-episode psychosis patients during two discrete periods before and after the introduction of an early intervention for psychosis service.
- All 465 patients had an objectively-rated diagnosis of first-episode psychosis using validated instruments.
- All participants had little or no antipsychotic exposure before the study.
- A limitation of the study is its retrospective nature, meaning some data were missing.
- Rates of adherence to international prescribing guidelines may be reflect the fact that they were not specifically promoted in this study setting.

INTRODUCTION

Early intervention for psychosis (EIP) has been shown to reduce illness severity, reduce hospitalisation and improve aspects of social functioning such as involvement in school or work.[1] Benefits are sustained in the short to medium term.[2 3] The components of an EIP service differ with regard to the specific interventions offered. Common themes, however, include use of medication, psychosocial interventions such as cognitive behavioural therapy (CBT), family interventions, rehabilitative interventions and psychoeducation.[1] EIP models of care also vary with some services delivered by specialist stand-alone multidisciplinary teams and others by enhanced community mental health teams (CMHT) whereby staff within CMHTs care for people with EIP in addition to their usual roles. 'Hub and spoke' models involve a centralised specialist 'hub' which supports specialist staff or 'spokes' embedded in local CMHTs.[4] Despite the variations in how the EIP services are delivered, recent evidence suggests that the early intervention approach is likely to be cost-effective.[5 6]

Antipsychotic medications are a key component of care for those experiencing psychosis. Response to a first antipsychotic medication in first episode psychosis (FEP) is high with up to 80% achieving a reduction in symptoms.[7] Maintenance treatment with antipsychotic medications reduces hospitalisations, improves life expectancy and enhances functional outcomes.[8-11] Given the evidence that no one agent has shown significant superiority in terms of efficacy in this population, [12] international guidelines recommend that tolerability should be the main influence when it comes to the choice of medication.[13] Clozapine is generally reserved for those who have not adequately responded to antipsychotic treatment, however lack of response should be identified early and clozapine initiated to improve outcomes.[13 14] Furthermore, doses of medication should also be lower in FEP than those used to treat later episodes of schizophrenia because people experiencing FEP are particularly sensitive to the effects and to the side effects of antipsychotic medication.

Pharmacological treatment guidelines have evolved over the lifetime of early intervention services with a notable change being the role of second generation antipsychotics (SGA). [15-17] The National Institute for Health and Care Excellence (NICE), for example, recommended SGAs as initial treatment in the early 2000's. Emerging evidence regarding the relative risks of SGAs, particularly metabolic risks, led to a change in the 2009 update of the NICE

guidelines with initial choice being driven by side effect profile rather than classification of antipsychotics.[17] The Patient Outcome Research Team (PORT) guidelines, also updated in 2009, specifically excluded olanzapine as a first line treatment option [16] and other guideline development groups have followed suit.[15 18] EIP services vary in their approach to medication with limited published information on prescriber training, treatment goals, algorithms or guidelines and delivery of treatment.[19] This is perhaps surprising given the evidence of sub-optimal use of antipsychotic medication in clinical practice.[20 21]

In this study we describe the pattern of antipsychotic medication use in two cohorts of FEP patients in the context of evolving clinical practice guidelines and the introduction of specialised EIP services. Our objectives were to determine (i) the adherence to international guideline recommendations on the initial choice and dose of antipsychotic medication (ii) whether a specific range of clinical or demographic factors at baseline were associated with the choice of medication or the initial dose of medication for patients supported by an EIP service.

METHODS

Study Design

The study is a retrospective examination of the medication prescribed for two cohorts of FEP patients before and after the introduction of EIP services. Data were gathered from clinical records, the EIP study database and electronic prescribing records. This article was written using the STROBE guidelines for reporting cohort studies.[22]

Study Setting

Data were extracted from a community based mental health service located in an urban area of south county Dublin with a current population of approximately 187,000. A large private hospital, located within the catchment area also participated in the study. EIP services were preceded by an epidemiological First Episode Study (FES) between 1995 and 1999.[23] Evidence from this study was used to secure funding for the Dublin and East Treatment and Early Care Team (DETECT). The specialist DETECT team offers rapid

assessment leading to phase specific psychological and family interventions. Antipsychotic medication use is managed by the patient's usual psychiatrist.

Participants and Inclusion Criteria

The FES cohort (C 1) was an epidemiologically complete sample recruiting all patients presenting in the catchment area with a first lifetime episode of psychosis between 1995 and 1999. Patients were included if they were aged 12 or over, gave consent to participate and had received less than 30 days antipsychotic treatment. Cases included in the DETECT cohort (C 2) were assessed by the EIP service between 2005 and 2016 and gave consent to participate in the study. Participants were aged between 16 and 65 and had received less than 30 days antipsychotic treatment before the EIP service assessment. The cohorts are described in Figure 1.

Assessments

Participants were included if they had a diagnosis of FEP based on the Structured Clinical Interview for DSM Axis I disorders (SCID).[24] The Global Assessment of Functioning scale (GAF) was used was used to rate subjectively social, occupational and psychological function. Scores range from 100 (extremely high functioning) to 1 (severe impairment).[25] For Cohort 1, psychological symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS).[26] The PANSS is scored by summation of individual items to produce positive symptom and negative symptom domain scores in a range of 7-49 and a composite general psychopathology score in the range of 16 to 112. The Scale for Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS), well established rating scales used in clinical research, were used to assess symptoms in C2.[27] SANS measures negative symptoms on a 25 item, 6-point scale. Items are listed under the five domains of affective blunting, alogia, avolition/apathy, anhedonia/asociality, and attention. SAPS measures positive symptoms on a 34 item, 6-point scale. Items are listed under hallucinations, delusions, bizarre behaviour, and positive formal thought disorder. All scales were administered by trained clinicians who participated with inter-rater reliability. Duration of untreated psychosis (DUP) was defined as the interval between first experience of psychotic symptom(s) and presentation to the

psychiatric services for initiation of treatment; first manic symptom(s) were used for bipolar disorder.[28]

Antipsychotic Prescribing Data

Prescribing data pertaining to C1 were compiled from paper charts. For the EIP cohort (C2), prescribing data at the time of clinical assessment (T1) was collected as part of a larger study of outcomes in first episode psychosis following the introduction of an EIP service. Medication at the time of initial assessment was recorded in the study database by the clinician carrying out the assessment. Data missing from the database and prescribing information following one month of engagement with the services (T2) were collected using hospital dispensing records and outpatient electronic prescribing records. Reports with details of prescription records were generated from the electronic health record separately using Discover Plus, a business intelligence software. It was taken that prescriptions generated within one week of the specified time points were the current medications. Cases for which no medication data were available were excluded.

Regular antipsychotic medication were included. Antipsychotics used for short periods on a 'pro re nata' (PRN) basis or for rapid tranquilisation were excluded. Where medications were being switched, we considered this to be appropriate polypharmacy and included the new antipsychotic as the choice assuming that the switch would be completed.

Doses of antipsychotic medication were categorised into 'low', $\leq$ 50% of the current British National Formulary (BNF) maximum dose; medium, $\geq$51% to $\leq$100% of current BNF maximum dose; and 'high' dose >100% of current BNF maximum dose. The rationale for this approach was based on pharmacological treatment guidelines which recommend doses at the lower end of the therapeutic dose range.[13] An exception to this was risperidone for which $\leq$6mgwas categorised as a 'low' dose in FEP based on guideline recommendations.[16] The current BNF dosing standards for haloperidol were applied but it should be noted that the BNF maximum dose has reduced over the lifetime of this study.

Statistical Methods

Initially, descriptive statistics were used to describe baseline characteristics and general prescribing patterns in both cohorts. Means and standard deviations (SD) are reported for

continuous variables and frequencies and percentages for categorical variables. For continuous scales which show evidence of or are expected to show some skew, a median and interquartile range (IQR) is also presented. Scatterplots were used to display trends in olanzapine prescribing over time and an indicator included at 2009 when guidelines were first published advising against the use of olanzapine as an initial medication in FEP. Univariate and multivariable logistic regression analysis was used to explore potential demographic and clinical associations with olanzapine use (yes/no), dose initiated (medium/high vs low) and also change in dose (increase vs the same or decreased) Demographic and clinical variables included in the models were age, gender, DUP, GAF, SAP, diagnosis and agitation symptoms. Statistical analysis was conducted using SPSS version 24 and Stata version 13

Ethics

Ethics approval was granted by the local research ethics committee.

Patient and Public Involvement

Patients and the public were not involved in this study.

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical baseline data from the FES (C1) are described in Table 1 and have previously been reported.[28] This was an epidemiologically complete sample and all people presenting with FEP consented to participate. Demographic and clinical characteristics for the EIP service (C2) were included for those who consented to participate in the study and for whom prescribing data were available (Table 1). Participants in both time periods were predominantly male with an average age of 28.5 (SD 11.1) years in the early cohort and 32.5 (SD 11.3) years in the EIP cohort. For both cohorts the majority were assessed in the inpatient setting and schizophrenia spectrum was the most common initial diagnosis (Table 1).

Table 1. Baseline description of demographic and clinical characteristics of two cohorts of patients presenting between 1995 -1999 and 2005-2016 for assessment of first episode psychosis prior to (C1) and after (C2) the introduction of an EIP service

	C 1 (1995 to 1999) N = 171			**C 2 (2005 to 2016) N = 319**
Gender	N (%)			N (%)
Male	99 (58)			189 (59.2)
Female	72 (42)			130 (40.8)
Age	Mean (SD)			Mean (SD)
	28.5 (11.1)			32.5 (11.3)
	N (%)			N (%)
Inpatient on assessment (%)	144 (84.2)			216 (67.7)
Initial Diagnosis[a]				
Schizophrenia Spectrum	101 (59.1)			124 (39.2)
Substance Induced Psychosis	12 (7)			45 (14.2)
Major Depressive Disorder	11 (6.4)			36 (11.4)
Bipolar Disorder	25 (14.6)			35 (11.1)
Delusional Disorder	13 (7.6)			35 (11.1)
Brief Psychotic Disorder	0			22 (7)
All other psychotic diagnoses	4 (5.2)			19 (6)
	Mean	Median	Range	Median (IQR)
DUP (months)[b]	17.9	5	0.25-240	3 (0.63 – 13)
GAF[c]	22.9			35 (30 - 48.5)
PANSS- Total [d]	74.4			
PANSS- Negative [e]	15.7			
PANSS- Positive [f]	21.3			
SAPS- Total [g]				18 (10-31)
SANS- Total [h]				12 (3-22)

IQR= Interquartile range; SD= Standard deviation

[a] 3 missing C2

[b] DUP= Estimated Duration of Untreated Psychosis. 5 missing C1; 156 missing C2

[c] GAF = Global Assessment of Functioning. 6 missing C2

[d] PANSS= Positive and Negative Symptom Scale Total Symptom Score

[e] PANSS- Negative = PANSS negative symptom score

[f] PANSS-Positive = PANSS positive symptom score

[g] SAPS- Total = Scale for Assessment of Positive Symptoms total score. 11 missing C2

[h] SANS- Total = Scale for Assessment of Negative Symptoms total score. 14 missing C2

Choice of Antipsychotic Medication

Prescribing data for a total of 465 patients were included, 146 in C1 and 319 in C2. Cases were excluded if prescribing data were not available for C1 (n=25) or if there were no prescribing data at time of initial assessment or one month follow up for C2. Prescribing patterns of antipsychotic medications are described in Table 2. The proportion of SGAs increased from 32.2% in C 1 to over 90% in C 2. FGA use predominated in C1 (65.1%), of which the most frequently chosen was sulpiride (19.2%), followed by thioridazine (11%) and haloperidol (10.3%). Olanzapine was the most frequently prescribed SGA throughout the time of the study and the prescribing frequency increased per year as represented in Figure 2. Guidelines published in 2009 advising against the use of olanzapine as an initial medication in FEP and widening the choice to first or second generation medicines did not appear to have an impact on prescribing patterns. Using C2 data, logistic regression analysis was used to explore demographic and clinical associations with olanzapine use (Table 3). Univariate analysis showed evidence of an association with GAF scale, in that for every unit increase in GAF scale, the odds of being on olanzapine, compared to no olanzapine, decreased (OR: 0.97; 95% CI: 0.95 to 0.99). However, there was no further evidence of associations with any other variables in univariate or multivariable analysis.

Table 2. Antipsychotic prescribing patterns among two cohorts of patients presenting for assessment of first episode psychosis before and after the introduction of an early intervention for psychosis service

	Cohort 1	**Cohort 2**	
	n=146	T1 (n=305)	T2 (n=293)
	N (%)	N (%)	N (%)
Second Generation			
Olanzapine	36 (24.7)	243 (79.7)	210 (71.7)
Risperidone (oral)	8 (5.5)	25 (8.2)	22 (7.5)
Amisulpride	2 (1.4)	7 (2.3)	11 (3.3)
Quetiapine	1 (0.7)	6 (2.0)	9 (2.7)
Aripiprazole		1 (0.3)	4 (1.4)
Risperidone LAI			3 (0.9)
Paliperidone (oral)			1 (0.3)
Paliperidone LAI			5 (1.5)
Second Generation Total	**47 (32.2)**	**282 (92.4)**	**265 (90.4)**
First Generation			
Sulpiride	28 (19.2)	1 (0.3)	1 (0.3)
Thioridazine	16 (11)	4 (1.3)	
Haloperidol	15 (10.3)		4 (1.4)
Chlorpromazine	13 (8.9)	3 (1)	1 (0.3)
Trifluoperazine	9 (6.2)	2 (0.7)	2 (0.6)
Flupenthixol Depot	4 (2.7)		1 (0.3)
Pimozide	4 (2.7)		1 (0.3)
Zuclopenthixol depot	1 (0.7)		5 (1.5)
Zuclopenthixol oral	1 (0.7)	1 (0.3)	
Flupenthixol (oral)	1 (0.7)	2 (0.7)	1 (0.4)
Fluphenazine	1 (0.7)		
Pipotiazine	1 (0.7)		
Perphenazine	1 (0.7)		
First Generation Total	**95 (65.1)**	**13 (4.3)**	**16 (5.5)**
No antipsychotic	4 (2.7)	10 (3.3)	12 (3.6)
T1 = Time of initial assessment T2 = One month following initial assessment LAI = Long acting injection			

Table 3. Regression analysis describing the odds of olanzapine use with reference to clinical and demographic characteristics for patients presenting to an EIP service.

	Univariate Analysis			Multivariable Analysis (n=142)	
	n	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age	295	1.02 (0.99 to 1.05)	0.14	1.04 (1.00 to 1.08)	0.06
DUP (months)	167	0.99 (0.97 to 1.01)	0.22	0.99 (0.97 to 1.01)	0.43
GAF	**291**	**0.97 (0.95 to 0.99)**	**0.02**	0.98 (0.94 to 1.01)	0.18
SAPS	289	1.06 (0.97 to 1.16)	0.18	1.00 (0.86 to 1.17)	0.97
Sex	295				
Male		1.00		1.00	
Female		0.82 (0.45 to 1.51)	0.53	0.68 (0.28 to 1.63)	0.39
Treatment	295				
Outpatient		1.00		1.00	
Inpatient		1.34 (0.72 to 2.51)	0.36	1.66 (0.66 to 4.19)	0.28
Diagnosis	292				
Affective		1.00		1.00	
Schizophreniform		0.54 (0.25 to 1.18)	0.12	1.04 (0.36 to 3.05)	0.94
All other Diagnoses		5.64 (0.69 to 46.39)	0.11	5.25 (0.53 to 52.08)	0.16
Agitation Symptoms	295				
present [a]		1.00		1.00	
not present [b]		1.25 (0.66 to 2.39)	0.50	0.86 (0.35 to 2.10)	0.74

DUP= Estimated Duration of Untreated Psychosis
GAF = Global Assessment of Functioning
SAPS = Scale for Assessment of Positive Symptoms
[a] Score of 2=mild, 3=moderate, 4= marked or 5= severe on the SAPS excitatory/agitation score
[b] Score of 0= none or 1= questionable on the SAPS excitatory/agitation score

Data were available for C2 showing that 10 (3.3%) patients at T1 and 11 (3.9%) patients at T2 were not prescribed antipsychotic medications. At initial assessment those who did not receive an antipsychotic medication had the following initial diagnoses: 'All other psychotic diagnosis' (n=4), substance induced psychosis, major depressive disorder (n=2), brief psychotic episode (n=2) and delusional disorder. However, this data was only identifiable for patients who received prescriptions for other medication on the electronic database and may be an underestimate.

Five patients were prescribed long acting injection or depot formulation of antipsychotic medication in C1. While no patient was initiated on a long acting injection (LAI) at initial presentation for C2, 14 (4.8%) had commenced an LAI by one month of treatment. Of the 319 cases in C2, data on both the medication used at initial assessment and at one month are available for 280 cases. Of these 35 (12.5%) patients required a switch of antipsychotic

medication within one month. Risperidone (n=6, 17.1%) was the most frequently used second choice antipsychotic followed by amisulpride (n=4, 11.4%) and quetiapine (n=3, 8.6%).

Dose of Antipsychotic Medication

Doses of medication at initial assessment were generally low in both cohorts (C1, 71% and C2, 78.6%). In this study, logistic regression was used to explore potential demographic and clinical associations with the odds of medium/high dose, compared to low dose (Table 4). Univariate analysis showed that the odds of medium/high dose, compared to low dose, was significantly higher for an inpatient compared to an outpatient (OR: 2.36; 95% CI: 1.09 to 5.11). No further evidence of associations with any other variables in univariate or multivariable analysis was seen.

Table 4. Regression analysis exploring the odds of medium or high dose antipsychotic use with reference to clinical and demographic characteristics for patients presenting to an EIP service.

		Univariate Analysis		Multivariable Analysis (n=142)	
	n	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Age	280	0.98 (0.95 to 1.01)	0.11	0.97 (0.93 to 1.01)	0.18
DUP (months)	154	0.97 (0.93 to 1.01)	0.09	0.98 (0.94 to 1.02)	0.23
GAF	276	1.00 (0.98 to 1.02)	0.81	0.99 (0.95 to 1.03)	0.50
SAPS	274	1.05 (0.96 to 1.14)	0.28	0.97 (0.82 to 1.15)	0.73
Sex	280				
Male		1.00		1.00	
Female		0.84 (0.45 to 1.57)	0.58	0.78 (0.28 to 2.14)	0.63
Treatment	280				
Outpatient		1.00		1.00	
Inpatient		**2.36 (1.09 to 5.11)**	**0.03**	2.83 (0.79 to 10.15)	0.11
Diagnosis	274				
Affective		1.00		1.00	
Schizophreniform		0.82 (0.39 to 1.73)	0.60	0.92 (0.29 to 2.98)	0.89
All other Diagnoses		1.83 (0.71 to 4.71)	0.21	2.17 (0.4 to 11.89)	0.37
Agitation Symptoms	290				
present [a]		1.00		1.00	
not present [b]		0.94 (0.49 to 1.78)	0.83	0.75 (0.26 to 2.17)	0.59

DUP= Estimated Duration of Untreated Psychosis
GAF = Global Assessment of Functioning
SAPS = Scale for Assessment of Positive Symptoms
[a] Score of 2=mild, 3=moderate, 4= marked or 5= severe on the SAPS excitatory/agitation score
[b] Score of 0= none or 1= questionable on the SAPS excitatory/agitation score

After one month of treatment the proportion of people in C2 requiring medium or high doses of medication increased from 17.9% to 42.7%. Of these, 4 patients (1.2%) were treated with doses above the BNF maximum, all of which were olanzapine at doses of 22.5 to 30mg per day.

Data on the dose of medication at both time points in C2 were available for 268 patients. Of these, 72 (26.8%) required an increase in dose over the first month of engagement with the early intervention service (Table 5). All of those who required an increase in dose had received an initial low dose of medication which was increased to a medium dose for 71 patients and a high dose for 1 patient. The dose of medication decreased for 10 (3.7%) people between initial assessment and following one month of engagement with the service. All 10 had been started on a medium dose of antipsychotic and the dose was reduced to a low dose over the first month. Medication was discontinued for one person who initially started on a low dose of medication. The dose for 186 people (69.4%) remained unchanged over the first month of engagement with the EIP service.

Table 5. Regression analysis exploring the odds of an increase in dose (compared with no increase - stay the same or decreased) with reference to clinical and demographic characteristics for patients presenting to an EIP service.

	Univariate Analysis			Multivariable Analysis (n=142)	
	n	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age	268	0.98 (0.96 to 1.00)	0.11	0.99 (0.95 to 1.03)	0.51
DUP (months)	147	0.99 (0.97 to 1.01)	0.37	1.00 (0.97 to 1.02)	0.76
GAF	263	0.97 (0.94 to 0.99)	<0.01	0.97 (0.93 to 1.01)	0.10
SAPS	262	1.13 (1.05 to 1.23)	<0.01	1.04 (0.89 to 1.21)	0.61
Sex	268				
Male		1.00		1.00	
Female		0.8 (0.46 to 1.40)	0.44	1.37 (0.57 to 3.29)	0.48
Treatment	268				
Outpatient		1.00		1.00	
Inpatient		2.10 (1.09 to 4.05)	0.03	1.76 (0.61 to 5.06)	0.30
Diagnosis	265				
Affective		1.00		1.00	
Schizophreniform		0.83 (0.43 to 1.61)	0.58	0.68 (0.23 to 2.01)	0.48
All other Diagnoses		1.13 (0.46 to 2.81)	0.79	1.43 (0.29 to 7.12)	0.67
Agitation Symptoms	263				
present [a]		1.00		1.00	
not present [b]		1.66 (0.95 to 2.91)	0.07	1.23 (0.5 to 3.06)	0.65

DUP= Estimated Duration of Untreated Psychosis
GAF = Global Assessment of Functioning
SAPS = Scale for Assessment of Positive Symptoms
[a] Score of 2=mild, 3=moderate, 4= marked or 5= severe on the SAPS excitatory/agitation score
[b] Score of 0= none or 1= questionable on the SAPS excitatory/agitation score

Univariate logistic regression analysis showed evidence that the odds of increasing a dose, compared to no increase (or a decrease), was significantly higher for an inpatient compared to an outpatient (OR: 2.10; 95% CI: 1.09 to 4.05, Table 5). Additionally, there was evidence of associations with GAF and SAPS. For every unit increase in GAF scale, the odds of an increase, compared to no increase, decreased (OR: 0.97; 95% CI: 0.94 to 0.99), and for every unit increase in SAPS the odds of an increase, compared to no increase, was 1.13 (95% CI: 1.05 to 1.23). However, they did not remain significant in the multivariable analysis. There was no further evidence of associations with any other variables in univariate or multivariable analysis (Table 5).

DISCUSSION

Summary of Findings

This study describes the pattern of antipsychotic prescribing for a naturalistic cohort of patients presenting for assessment of FEP in a geographically defined catchment over a 21 year period. The data demonstrate the changes over time in the choice of antipsychotic medication, the move towards predominantly second generation antipsychotic use and the prevalence of olanzapine as a first choice medication. Guidelines issued in both Europe and America widening the choice of antipsychotic medication or specifically not recommending olanzapine as an initial choice of agent do not appear to have had an impact on prescribing patterns. Additional indicators of good practice such as the use of low doses of antipsychotic medication for the initial treatment of FEP and the avoidance of high doses and antipsychotic polypharmacy are demonstrated. The demographic and clinical factors investigated did not appear to significantly influence the initial choice of antipsychotic medication. There was some evidence that inpatient treatment setting was associated with a higher initial dose of antipsychotic medication (>50% BNF maximum). Increasing dose requirements over the first month of engagement with an EIP service was associated with poorer global functioning at baseline, greater positive symptoms at baseline and the inpatient treatment setting. However, these associations were not seen in the multivariable model.

Comparison with Previous Literature and Clinical Implications

EIP services aim to provide timely access to comprehensive assessment and programmes of care including medical, psychological, occupational and social support.[29] A positive first experience of using antipsychotic medicines is likely to have an impact on future engagement with services and outcomes.[30 31] Careful consideration of the first antipsychotic medication involves balancing side effects with expected benefits and incorporating the patient perspective through a shared decision making approach. Managing side effects, is a significant challenge with the risks of metabolic abnormalities, sexual problems and movement disorders among the many potential disadvantages of using these medications. Given the variety of antipsychotic medication available, the lack of evidence for relative

efficacy benefits in FEP in the context of significant differences in side effect profiles,[12] it is useful to examine what medications are actually used in practice with clinical implications for the services' approach to managing physical health complications of antipsychotic use.

The trend towards SGA use over time in our study reflects the early optimism for medications with reduced propensity to cause anticholinergic side effects and long term movement disorders. While the preference for olanzapine as a first choice antipsychotic has been previously been reported in the literature.[32-35] the prescribing rate in this cohort are high by comparison. For example, a Spanish study of prescribing practices for FEP found that 22.7% were prescribed olanzapine and a UK study described a prescribing rate of 35%. In the United States ,where the PORT guidelines specifically exclude olanzapine as a first choice medication the prescribing rate was 31.2% in the Recovery After an Initial Schizophrenia Episode-Early Treatment Programme (RAISE-ETP) study.[20] Although this study did not explore the reasons for clinicians' choice of antipsychotic medication, olanzapine may be perceived to be more effective[36] and reduce the need for additional prescribing e.g. a benzodiazepine or hypnotic.

Olanzapine has a higher risk of inducing weight gain and metabolic abnormalities in comparison to other antipsychotics that could potentially be used as an initial treatment option in FEP.[37 38] Antipsychotic induced weight gain causes considerable patient distress, has serious general health implications and leads to early discontinuation of medication.[39] Over time the characteristics of the population changed with more people provisionally diagnosed with substance use disorder in comparison to the early cohort. This likely reflects the achievements of the EIP service in reducing DUP and the diagnostic criteria for schizophrenia requiring presence of symptoms for six months or more. Olanzapine is a sedative medicine and may be a reasonable choice if the patient were agitated, a presentation commonly associated with substance misuse. However, univariate and multivariate regression did not find an association with symptoms of agitation. While a reduction in the proportion of FEP patients using olanzapine as an initial treatment could be beneficial, strategies to prevent and manage weight gain should form part of an EIP programme where olanzapine continues to be used as a first line agent. Lifestyle interventions [40], metformin [41] or liraglutide [42] are potential options.

Historically LAI and depot formulations were recommended if adherence to oral medication was poor[13] or, in more recent times, as first line agents if the patient expressed a preference for the formulation.[43] The advantages may include reduced hospitalisation, more stable therapeutic blood levels with no additional side effect burden and, convenience for the patient.[43 44] Confirming adherence through the use of LAIs may lead to better treatment decisions and earlier recognition of treatment resistance. However, barriers to the use of these formulations include a reluctance on the part of some patients to engage in their use and a view that there may be a coercive nature to injecting medication.[45] In this study the prevalence of LAI use is low, with some historical use of the FGA's described in our first cohort. The preference for SGA's may have had an impact on the use of LAI's until the development of the first second generation LAI formulation of risperidone.

Clozapine is generally reserved for patients whose symptoms have not responded to adequate trials of two antipsychotic medication at the maximum tolerable dose.[13 46] When compared to chlorpromazine as an initial treatment for FEP, clozapine was no more effective.[47] However, early use of clozapine for those considered treatment resistant has been recognised as increasingly important. For example, early use of clozapine was effective for 75% of those with treatment resistance included in an observational study by Agid *et al*. Furthermore, Yoshimura *et al* report that early use of clozapine was associated with a response rate of 80% compared with a response rate of 30% if clozapine initiation was delayed by 2.8 years or more.[48] In our study none of the patients were treated with clozapine and this is likely due to the inclusion of patients in the very early stages of treatment with up to 30 days antipsychotic exposure at study entry. Additional research has demonstrated that the time to clozapine treatment for those with treatment resistant illness in our study cohorts is reducing with an average time to clozapine treatment of 6.7 years in the FEP study[49] compared with 2.1 years for those engaged in the EIP service.[50]

Guidelines recommend commencing antipsychotic medication at the lower half of the dose range in FEP.[16 17] We therefore took a pragmatic approach to describing the pattern of antipsychotic doses by expressing dose as a percentage of the BNF maximum. Guideline recommendations were generally adhered to with 78.6% of patients prescribed lower doses at initial presentation and the use of high dose medication regimens was negligible at both initial assessment and after one month of treatment. Bioque *et al* reported that 8.9% of

patients received higher doses of medication, by comparison.[34] Our description of antipsychotic use in the very early stages of treatment for FEP may explain the low rates of antipsychotic polypharmacy and high dose treatment strategies in comparison to other studies.[34 51]

Clinical practice guidelines in psychiatry are often difficult to implement.[21 52] In the RAISE-ETP study, for example, Robinson *et al* found that, at the point of engagement with an EIP service, medication review would be beneficial for 39.4% of the 404 patients enrolled in their study. The reasons for medication review included the use of olanzapine (31.2%) and the use of high dose regimens (8.8%) or combinations of antipsychotic medications (23.3%).[51]Proactive support for prescribing practice can be an effective means of improving the quality of medication use in first episode psychosis.[19 48 53] Observational studies by Yoshimura *et al* and Yeisen *et al* demonstrated that the initial choice of antipsychotic can be influenced by locally implemented algorithms.[48 53] Robinson *et al* developed the NAVIGATE prescribing principals and the COMPASS decision making tool which was designed to facilitate communication between the patient and the prescriber in the RAISE trial.[19] Training was provided for prescribers and they were given ongoing support throughout the study. Over a 2 year period study participants (n=223) had more medication visits, were more likely to use a medication that conformed to the NAVIGATE guidelines, experienced fewer side effects and gained less weight than those who has received usual community care (n=181). Adherence estimator scores also improved in the NAGIGATE group but not in the community group. The models of care for EIS internationally give varying attention to supporting medicines optimisation.[1] This evidence and the results of our study suggest that EIP services and patients could benefit from proactive support for prescribing practice.

Strengths, Limitations and Future Research

We report prescribing data from a naturalistic cohort with inclusion criteria reflecting the age range and diagnoses presenting to an EIP service. The longitudinal data allow a view of the pattern of prescribing practice over a 21 year period during the development and implementation of an EIP service. We were also able to describe the clinical use of the medications in terms of dose changes and the need to switch medication or formulation over the first month of engagement with the EIP service. In studies regarding antipsychotic use in an FEP population, patients were often treated with antipsychotic medication for a number of months before assessment by an EIP service and therefore may not accurately reflect the first choice of antipsychotic or initial dose.[32 34 35 51] In our study, participants had less than 30 days antipsychotic exposure.

Patient related factors other than those assessed, such as patient preference sociodemographic factors or clinical metabolic parameters, may have had an influence on the choice or dose of antipsychotic medication. While we were able to describe the choice of antipsychotic when switching medication, we did not have the data to explore the reasons for switching medication. The retrospective nature of this study led to some missing data in both cohorts. The pattern of prescribing in the interim period between the FES and the EIP studies could not be described. International prescribing guidelines are not specifically promoted in Ireland and there are no local antipsychotic prescribing guidelines for FEP in the Irish mental health services. Their influence may, therefore, be expected to be poor. It would be useful to examine the topic prospectively to include shared decision making processes and clinician related factors and investigate the impact on patient outcomes including physical health. Future local or national guidelines may influence prescribing practice and include decision support tools and proactive management protocols to mitigate the potential side effects of antipsychotic medication.

CONCLUSION

There is clearly a move toward the use of SGAs as initial treatment for FEP. Guidelines which recommend avoiding olanzapine as an initial choice based on its side effect profile, do not appear to have had an influence on prescribing practice. Antipsychotics are generally initiated at low doses. Given the importance of early experiences with medication consideration should be given to including a proactive approach to medicines optimisation within the EIP model of care. This could include locally agreed guidelines, decision support tools for both patients and clinicians and active management of side effects.

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CONTRIBUTIONS

DK designed and conducted the study in collaboration with JS and MC. DK extracted the data for the DETECT cohort from the DETECT research database and hospital prescribing records. RD and CB extracted the data in relation to the first episode study. DK analysed the data with advice from FB. DK wrote the manuscript with input from SMcW, FB, JS and MC.

COMPETING INTERESTS

The authors report no competing interests

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DATA SHARING STATEMENT

Anonymised participant data is held in a secure research server and will be handled in accordance with the ethical approval for this project.

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Figures

Figure 1. Description of cohorts of patients presenting to an early intervention service, timeframe of presentation, inclusion criteria, demographic and medication related variables

[a]Duration of Untreated Psychosis; [b]Structured Clinical Interview for Diagnosis; [c]Positive and Negative Symptom Scale; [d]Global Assessment of Functioning; [e]Scale for Assessment of Positive Symptoms; [f]Scale for Assessment of Negative Symptoms

Figure 2. Proportion of olanzapine (%) prescribed per year for patients presenting for assessment of first episode psychosis. Guidelines published in 2009 advising against the use of olanzapine as an initial medication in FEP and widening the choice to first or second generation antipsychotics (orange line).

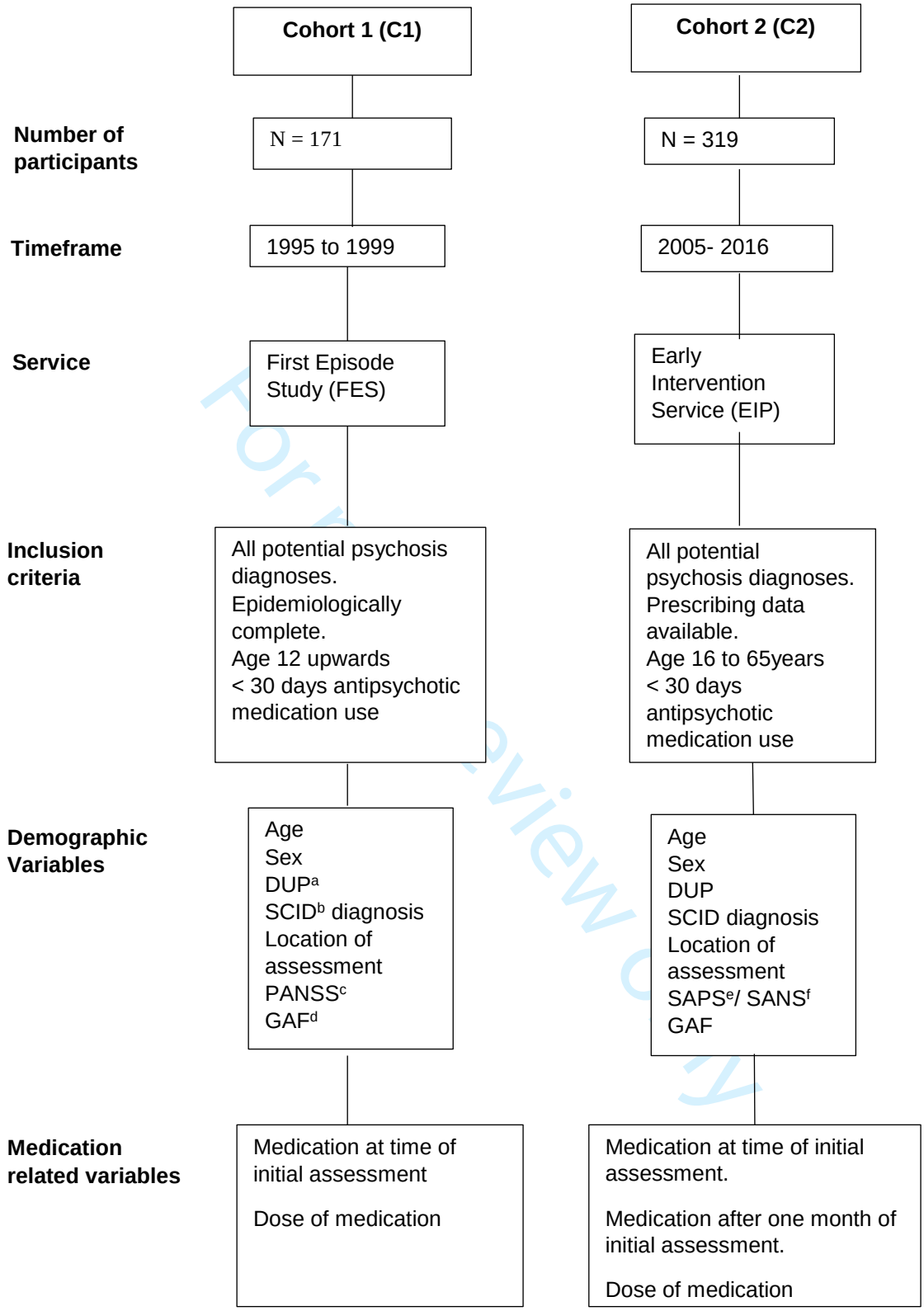

Figure 1. Description of cohorts of patients presenting to an early intervention service, timeframe of presentation, inclusion criteria, demographic and medication related variables

[a]Duration of Untreated Psychosis; [b]Structured Clinical Interview for Diagnosis; [c]Positive and Negative Symptom Scale; [d]Global Assessment of Functioning; [e]Scale for Assessment of Positive Symptoms; [f]Scale for Assessment of Negative Symptoms

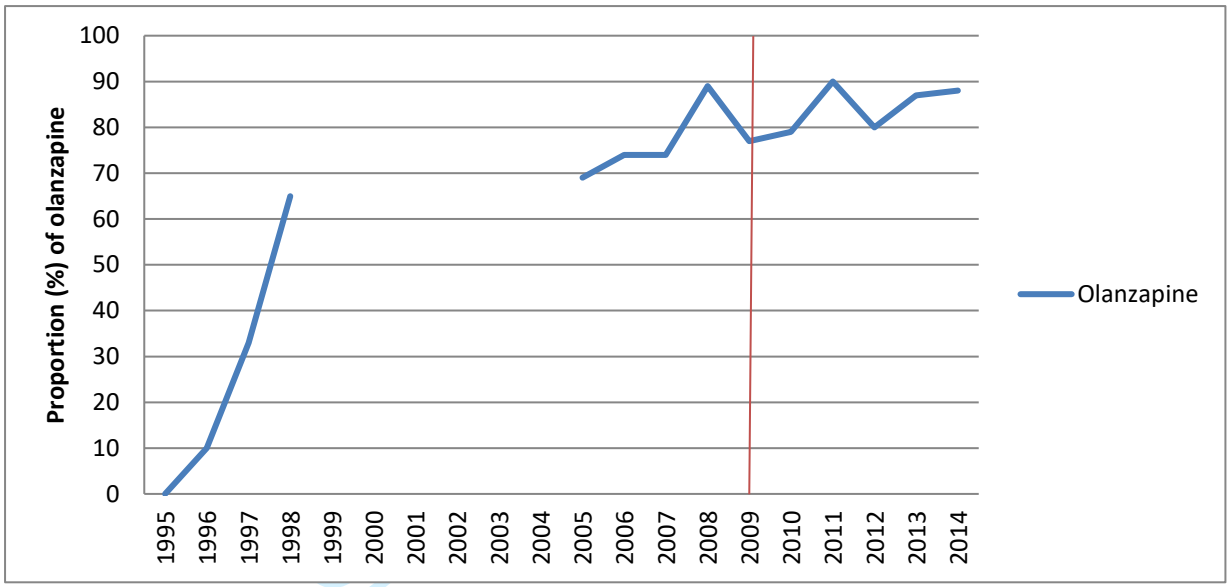

Figure 2 Proportion of olanzapine (%) prescribed per year for patients presenting for assessment of first episode psychosis

Guidelines published in 2009 advising against the use of olanzapine as an initial medication in FEP and widening the choice to first or second generation antipsychotics (orange line).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8,9
		(b) Give reasons for non-participation at each stage	8,9
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	10,11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-17
		(*b*) Report category boundaries when continuous variables were categorized	10-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prescribing Pattern of Antipsychotic Medication for First Episode Psychosis: A Retrospective Cohort Study

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Prescribing Pattern of Antipsychotic Medication for First Episode Psychosis: A Retrospective Cohort Study

Dolores Keating PhD[1,2], Stephen McWilliams MD[3,4], Fiona Boland PhD[5], Roisin Doyle MSc[6], Caragh Behan PhD[7], Judith Strawbridge PhD[2] and Mary Clarke MD [4,6]

Corresponding author:

Dr Dolores Keating, [1]Pharmacy Department, Saint John of God Hospital, Stillorgan, Co Dublin, Ireland;

[2]School of Pharmacy, Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin 2.

Tel +35312771607. Email Dolores.keating@sjog.ie

Co-authors

Dr Stephen McWilliams, [3]Saint John of God Hospital, Stillorgan, Co Dublin, Ireland

[4]School of Medicine, University College Dublin, Dublin 4.

Dr. Fiona Boland, [5]Data Science centre and HRB Centre for Primary Care Research, Royal College of Surgeons in Ireland, 123 St Stephens Green, Dublin 2, Ireland

Roisin Doyle, [6]DETECT Early Intervention in Psychosis Service, Blackrock, Co Dublin, Ireland

Dr Caragh Behan, [7]Cluain Mhuire Services, Newtownpark Avenue, Blackrock, Co Dublin

Prof Judith Strawbridge, [2]School of Pharmacy, Royal College of Surgeons in Ireland, 123 St Stephen's Green, Dublin 2.

Prof Mary Clarke, [6]DETECT Early Intervention in Psychosis Service, Blackrock, Co Dublin, Ireland

[4]School of Medicine, University College Dublin, Dublin 4.

Keywords: First Episode Psychosis, Antipsychotic, Guideline

Word Count: 4437

ABSTRACT

Objective

Guidelines for antipsychotic use in first-episode psychosis (FEP) recommend that medication be chosen initially on the basis of side-effect profile with doses at the lower end of the range. Our objective was to describe the pattern of antipsychotic use in FEP over a period of 21 years in the context of changing clinical guidelines and the development of specialist Early Intervention for Psychosis (EIP) services.

Setting

A community-based mental health service in south County Dublin (population 187,000) and a large private hospital.

Participants

Participants included 465 FEP patients [146 from an epidemiological study (1995-1999) and 319 from a specialist early intervention for psychosis (EIP) service (2005-2016). Treatment with antipsychotic medication did not exceed 30 days at study entry.

Outcome Measures

This is a descriptive study of prescribing practices in the context of service development and changing guidelines.

Results

First-generation antipsychotics were prescribed for 65% of the early cohort compared with 4.3% of the EIP cohort. Olanzapine was initially prescribed for 79.7% of EIP patients. Initial doses of medication were frequently low (≤ 50% BNF maximum) in both cohorts (71% and 78.6%). The demographic and clinical factors investigated did not influence the initial choice of antipsychotic medication significantly. Univariate logistic regression analysis suggested inpatient treatment setting was associated with a higher initial dose (>50% BNF maximum) of antipsychotic medication. Increasing dose requirements over the first month of engagement with an EIP service was associated with poorer global functioning at baseline, greater positive symptoms at baseline and the inpatient treatment setting. However, these associations were not seen in the multivariable model.

Conclusions

Second-generation antipsychotic prescribing predominates, but guidelines are often overlooked when choosing olanzapine notwithstanding lower initial dosages. EIP services should include proactive support for optimising medicines in line with evidence-based guidelines.

STRENGTHS AND LIMITATIONS OF THE STUDY

- This 21 year study describes antipsychotic prescribing practices for a naturalistic cohort of first-episode psychosis patients during two discrete periods before and after the introduction of an early intervention for psychosis service.
- All 465 patients had an objectively-rated diagnosis of first-episode psychosis using validated instruments.
- All participants had little or no antipsychotic exposure before the study.
- A limitation of the study is its retrospective nature, meaning some data were missing.
- Rates of adherence to international prescribing guidelines may be reflect the fact that they were not specifically promoted in this study setting.

INTRODUCTION

Early intervention for psychosis (EIP) has been shown to reduce illness severity, reduce hospitalisation and improve aspects of social functioning such as involvement in school or work.[1] Benefits are sustained in the short to medium term.[2 3] The components of an EIP service differ with regard to the specific interventions offered. Common themes, however, include use of medication, psychosocial interventions such as cognitive behavioural therapy (CBT), family interventions, rehabilitative interventions and psychoeducation.[1] EIP models of care also vary with some services delivered by specialist stand-alone multidisciplinary teams and others by enhanced community mental health teams (CMHT) whereby staff within CMHTs care for people with EIP in addition to their usual roles. 'Hub and spoke' models involve a centralised specialist 'hub' which supports specialist staff or 'spokes' embedded in local CMHTs.[4] Despite the variations in how the EIP services are delivered, recent evidence suggests that the early intervention approach is likely to be cost-effective.[5 6]

Antipsychotic medications are a key component of care for those experiencing psychosis. Response to a first antipsychotic medication in first episode psychosis (FEP) is high with up to 80% achieving a reduction in symptoms.[7] Maintenance treatment with antipsychotic medications reduces hospitalisations, improves life expectancy and enhances functional outcomes.[8-11] Given the evidence that no one agent has shown significant superiority in terms of efficacy in this population, [12] international guidelines recommend that tolerability should be the main influence when it comes to the choice of medication.[13] Clozapine is generally reserved for those who have not adequately responded to antipsychotic treatment, however lack of response should be identified early and clozapine initiated to improve outcomes.[13 14] Furthermore, doses of medication should also be lower in FEP than those used to treat later episodes of schizophrenia because people experiencing FEP are particularly sensitive to the effects and to the side effects of antipsychotic medication.

Pharmacological treatment guidelines have evolved over the lifetime of early intervention services with a notable change being the role of second generation antipsychotics (SGA). [15-17] The National Institute for Health and Care Excellence (NICE), for example, recommended SGAs as initial treatment in the early 2000's. Emerging evidence regarding the relative risks of SGAs, particularly metabolic risks, led to a change in the 2009 update of the NICE

guidelines with initial choice being driven by side effect profile rather than classification of antipsychotics.[17] The Patient Outcome Research Team (PORT) guidelines, also updated in 2009, specifically excluded olanzapine as a first line treatment option [16] and other guideline development groups have followed suit.[15 18] EIP services vary in their approach to medication with limited published information on prescriber training, treatment goals, algorithms or guidelines and delivery of treatment.[19] This is perhaps surprising given the evidence of sub-optimal use of antipsychotic medication in clinical practice.[20 21]

In this study we describe the pattern of antipsychotic medication use in two cohorts of FEP patients in the context of evolving clinical practice guidelines and the introduction of specialised EIP services. Our objectives were to determine (i) the adherence to international guideline recommendations on the initial choice and dose of antipsychotic medication (ii) whether a specific range of clinical or demographic factors at baseline were associated with the choice of medication or the initial dose of medication for patients supported by an EIP service.

METHODS

Study Design

The study is a retrospective examination of the medication prescribed for two cohorts of FEP patients before and after the introduction of EIP services. Data were gathered from clinical records, the EIP study database and electronic prescribing records. This article was written using the STROBE guidelines for reporting cohort studies.[22]

Study Setting

Data were extracted from a community based mental health service located in an urban area of south county Dublin with a current population of approximately 187,000. A large private hospital, located within the catchment area also participated in the study. EIP services were preceded by an epidemiological First Episode Study (FES) between 1995 and 1999.[23] Evidence from this study was used to secure funding for the Dublin and East Treatment and Early Care Team (DETECT). The specialist DETECT team offers rapid

assessment leading to phase specific psychological and family interventions. Antipsychotic medication use is managed by the patient's usual psychiatrist.

Participants and Inclusion Criteria

The FES cohort (C 1) was an epidemiologically complete sample recruiting all patients presenting in the catchment area with a first lifetime episode of psychosis between 1995 and 1999. Patients were included if they were aged 12 or over, gave consent to participate and had received less than 30 days antipsychotic treatment. Cases included in the DETECT cohort (C 2) were assessed by the EIP service between 2005 and 2016 and gave consent to participate in the study. Participants were aged between 16 and 65 and had received fewer than 30 days antipsychotic treatment before the EIP service assessment. At the time of assessment, informed consent was given by parents or guardians for all participants' aged under 18 years in line with the study protocol and the requirements of the ethics committee. The cohorts are described in Figure 1.

Assessments

Participants were included if they had a diagnosis of FEP based on the Structured Clinical Interview for DSM Axis I disorders (SCID).[24] The Global Assessment of Functioning scale (GAF) was used was used to rate subjectively social, occupational and psychological function. Scores range from 100 (extremely high functioning) to 1 (severe impairment).[25] For Cohort 1, psychological symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS).[26] The PANSS is scored by summation of individual items to produce positive symptom and negative symptom domain scores in a range of 7-49 and a composite general psychopathology score in the range of 16 to 112. The Scale for Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS), well established rating scales used in clinical research, were used to assess symptoms in C2.[27] SANS measures negative symptoms on a 25 item, 6-point scale. Items are listed under the five domains of affective blunting, alogia, avolition/apathy, anhedonia/asociality, and attention. SAPS measures positive symptoms on a 34 item, 6-point scale. Items are listed under hallucinations, delusions, bizarre behaviour, and positive formal thought disorder. All scales were administered by trained clinicians who participated with inter-rater reliability. Duration of untreated psychosis (DUP) was defined as the

interval between first experience of psychotic symptom(s) and presentation to the psychiatric services for initiation of treatment; first manic symptom(s) were used for bipolar disorder.[28]

Antipsychotic Prescribing Data

Prescribing data pertaining to C1 were compiled from paper charts. For the EIP cohort (C2), prescribing data at the time of clinical assessment (T1) was collected as part of a larger study of outcomes in first episode psychosis following the introduction of an EIP service. Medication at the time of initial assessment was recorded in the study database by the clinician carrying out the assessment. Data missing from the database and prescribing information following one month of engagement with the services (T2) were collected using hospital dispensing records and outpatient electronic prescribing records. Reports with details of prescription records were generated from the electronic health record separately using Discover Plus, a business intelligence software. It was taken that prescriptions generated within one week of the specified time points were the current medications. Cases for which no medication data were available were excluded.

Regular antipsychotic medication were included. Antipsychotics used for short periods on a 'pro re nata' (PRN) basis or for rapid tranquilisation were excluded. Where medications were being switched, we considered this to be appropriate polypharmacy and included the new antipsychotic as the choice assuming that the switch would be completed.

Doses of antipsychotic medication were categorised into 'low', ≤ 50% of the current British National Formulary (BNF) maximum dose; medium, ≥51% to ≤100% of current BNF maximum dose; and 'high' dose >100% of current BNF maximum dose. The rationale for this approach was based on pharmacological treatment guidelines which recommend doses at the lower end of the therapeutic dose range.[13] An exception to this was risperidone for which ≤6mgwas categorised as a 'low' dose in FEP based on guideline recommendations.[16] The current BNF dosing standards for haloperidol were applied but it should be noted that the BNF maximum dose has reduced over the lifetime of this study.

Statistical Methods

Initially, descriptive statistics were used to describe baseline characteristics and general prescribing patterns in both cohorts. Means and standard deviations (SD) are reported for continuous variables and frequencies and percentages for categorical variables. For continuous scales which show evidence of or are expected to show some skew, a median and interquartile range (IQR) is also presented. Scatterplots were used to display trends in olanzapine prescribing over time and an indicator included at 2009 when guidelines were first published advising against the use of olanzapine as an initial medication in FEP. Univariate and multivariable logistic regression analysis was used to explore potential demographic and clinical associations with olanzapine use (yes/no), dose initiated (medium/high vs low) and also change in dose (increase vs the same or decreased) Demographic and clinical variables included in the models were age, gender, DUP, GAF, SAP, diagnosis and agitation symptoms. Statistical analysis was conducted using SPSS version 24 and Stata version 13

Ethics

Ethics approval was granted by the Saint John of God Hospitaller Services Research Ethics Committee.

Patient and Public Involvement

Patients and the public were not involved in this study.

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical baseline data from the FES (C1) are described in Table 1 and have previously been reported.[28] This was an epidemiologically complete sample and all people presenting with FEP consented to participate. Demographic and clinical characteristics for the EIP service (C2) were included for those who consented to participate in the study and for whom prescribing data were available (Table 1). Participants in both time periods were

predominantly male with an average age of 28.5 (SD 11.1) years in the early cohort and 32.5 (SD 11.3) years in the EIP cohort. For both cohorts the majority were assessed in the inpatient setting and schizophrenia spectrum was the most common initial diagnosis (Table 1).

Table 1. Baseline description of demographic and clinical characteristics of two cohorts of patients presenting between 1995 -1999 and 2005-2016 for assessment of first episode psychosis prior to (C1) and after (C2) the introduction of an EIP service

	C 1 (1995 to 1999) N = 171			**C 2 (2005 to 2016) N = 319**
Gender	N (%)			N (%)
Male	99 (58)			189 (59.2)
Female	72 (42)			130 (40.8)
Age	Mean (SD)			Mean (SD)
	28.5 (11.1)			32.5 (11.3)
	N (%)			N (%)
Inpatient on assessment (%)	144 (84.2)			216 (67.7)
Initial Diagnosis[a]				
Schizophrenia Spectrum	101 (59.1)			124 (39.2)
Substance Induced Psychosis	12 (7)			45 (14.2)
Major Depressive Disorder	11 (6.4)			36 (11.4)
Bipolar Disorder	25 (14.6)			35 (11.1)
Delusional Disorder	13 (7.6)			35 (11.1)
Brief Psychotic Disorder	0			22 (7)
All other psychotic diagnoses	4 (5.2)			19 (6)
	Mean	Median	Range	Median (IQR)
DUP (months)[b]	17.9	5	0.25-240	3 (0.63 – 13)
GAF[c]	22.9			35 (30 - 48.5)
PANSS- Total [d]	74.4			
PANSS- Negative [e]	15.7			
PANSS- Positive [f]	21.3			
SAPS- Total [g]				18 (10-31)
SANS- Total [h]				12 (3-22)

IQR= Interquartile range; SD= Standard deviation

[a] 3 missing C2

[b] DUP= Estimated Duration of Untreated Psychosis. 5 missing C1; 156 missing C2

[c] GAF = Global Assessment of Functioning. 6 missing C2

[d] PANSS= Positive and Negative Symptom Scale Total Symptom Score

[e] PANSS- Negative = PANSS negative symptom score

[f] PANSS-Positive = PANSS positive symptom score

[g] SAPS- Total = Scale for Assessment of Positive Symptoms total score. 11 missing C2

[h] SANS- Total = Scale for Assessment of Negative Symptoms total score. 14 missing C2

Choice of Antipsychotic Medication

Prescribing data for a total of 465 patients were included, 146 in C1 and 319 in C2. Cases were excluded if prescribing data were not available for C1 (n=25) or if there were no prescribing data at time of initial assessment or one month follow up for C2. Prescribing patterns of antipsychotic medications are described in Table 2. The proportion of SGAs increased from 32.2% in C 1 to over 90% in C 2. FGA use predominated in C1 (65.1%), of which the most frequently chosen was sulpiride (19.2%), followed by thioridazine (11%) and haloperidol (10.3%). Olanzapine was the most frequently prescribed SGA throughout the time of the study and the prescribing frequency increased per year as represented in Figure 2. Guidelines published in 2009 advising against the use of olanzapine as an initial medication in FEP and widening the choice to first or second generation medicines did not appear to have an impact on prescribing patterns. Using C2 data, logistic regression analysis was used to explore demographic and clinical associations with olanzapine use (Table 3). Univariate analysis showed evidence of an association with GAF scale, in that for every unit increase in GAF scale, the odds of being on olanzapine, compared to no olanzapine, decreased (OR: 0.97; 95% CI: 0.95 to 0.99). However, there was no further evidence of associations with any other variables in univariate or multivariable analysis.

Table 2. Antipsychotic prescribing patterns among two cohorts of patients presenting for assessment of first episode psychosis before and after the introduction of an early intervention for psychosis service

	Cohort 1	**Cohort 2**	
	n=146	T1 (n=305)	T2 (n=293)
	N (%)	N (%)	N (%)
Second Generation			
Olanzapine	36 (24.7)	243 (79.7)	210 (71.7)
Risperidone (oral)	8 (5.5)	25 (8.2)	22 (7.5)
Amisulpride	2 (1.4)	7 (2.3)	11 (3.3)
Quetiapine	1 (0.7)	6 (2.0)	9 (2.7)
Aripiprazole		1 (0.3)	4 (1.4)
Risperidone LAI			3 (0.9)
Paliperidone (oral)			1 (0.3)
Paliperidone LAI			5 (1.5)
Second Generation Total	**47 (32.2)**	**282 (92.4)**	**265 (90.4)**
First Generation			
Sulpiride	28 (19.2)	1 (0.3)	1 (0.3)
Thioridazine	16 (11)	4 (1.3)	
Haloperidol	15 (10.3)		4 (1.4)
Chlorpromazine	13 (8.9)	3 (1)	1 (0.3)
Trifluoperazine	9 (6.2)	2 (0.7)	2 (0.6)
Flupenthixol Depot	4 (2.7)		1 (0.3)
Pimozide	4 (2.7)		1 (0.3)
Zuclopenthixol depot	1 (0.7)		5 (1.5)
Zuclopenthixol oral	1 (0.7)	1 (0.3)	
Flupenthixol (oral)	1 (0.7)	2 (0.7)	1 (0.4)
Fluphenazine	1 (0.7)		
Pipotiazine	1 (0.7)		
Perphenazine	1 (0.7)		
First Generation Total	**95 (65.1)**	**13 (4.3)**	**16 (5.5)**
No antipsychotic	4 (2.7)	10 (3.3)	12 (3.6)
T1 = Time of initial assessment T2 = One month following initial assessment LAI = Long acting injection			

Table 3. Regression analysis describing the odds of olanzapine use with reference to clinical and demographic characteristics for patients presenting to an EIP service.

	Univariate Analysis			Multivariable Analysis (n=142)	
	n	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age	295	1.02 (0.99 to 1.05)	0.14	1.04 (1.00 to 1.08)	0.06
DUP (months)	167	0.99 (0.97 to 1.01)	0.22	0.99 (0.97 to 1.01)	0.43
GAF	**291**	**0.97 (0.95 to 0.99)**	**0.02**	0.98 (0.94 to 1.01)	0.18
SAPS	289	1.06 (0.97 to 1.16)	0.18	1.00 (0.86 to 1.17)	0.97
Sex	295				
Male		1.00		1.00	
Female		0.82 (0.45 to 1.51)	0.53	0.68 (0.28 to 1.63)	0.39
Treatment	295				
Outpatient		1.00		1.00	
Inpatient		1.34 (0.72 to 2.51)	0.36	1.66 (0.66 to 4.19)	0.28
Diagnosis	292				
Affective		1.00		1.00	
Schizophreniform		0.54 (0.25 to 1.18)	0.12	1.04 (0.36 to 3.05)	0.94
All other Diagnoses		5.64 (0.69 to 46.39)	0.11	5.25 (0.53 to 52.08)	0.16
Agitation Symptoms	295				
present [a]		1.00		1.00	
not present [b]		1.25 (0.66 to 2.39)	0.50	0.86 (0.35 to 2.10)	0.74

DUP= Estimated Duration of Untreated Psychosis
GAF = Global Assessment of Functioning
SAPS = Scale for Assessment of Positive Symptoms
[a] Score of 2=mild, 3=moderate, 4= marked or 5= severe on the SAPS excitatory/agitation score
[b] Score of 0= none or 1= questionable on the SAPS excitatory/agitation score

Data were available for C2 showing that 10 (3.3%) patients at T1 and 11 (3.9%) patients at T2 were not prescribed antipsychotic medications. At initial assessment those who did not receive an antipsychotic medication had the following initial diagnoses: 'All other psychotic diagnosis' (n=4), substance induced psychosis, major depressive disorder (n=2), brief psychotic episode (n=2) and delusional disorder. However, this data was only identifiable for patients who received prescriptions for other medication on the electronic database and may be an underestimate.

Five patients were prescribed long acting injection or depot formulation of antipsychotic medication in C1. While no patient was initiated on a long acting injection (LAI) at initial presentation for C2, 14 (4.8%) had commenced an LAI by one month of treatment. Of the 319 cases in C2, data on both the medication used at initial assessment and at one month are available for 280 cases. Of these 35 (12.5%) patients required a switch of antipsychotic

medication within one month. Risperidone (n=6, 17.1%) was the most frequently used second choice antipsychotic followed by amisulpride (n=4, 11.4%) and quetiapine (n=3, 8.6%).

Dose of Antipsychotic Medication

Doses of medication at initial assessment were generally low in both cohorts (C1, 71% and C2, 78.6%). In this study, logistic regression was used to explore potential demographic and clinical associations with the odds of medium/high dose, compared to low dose (Table 4). Univariate analysis showed that the odds of medium/high dose, compared to low dose, was significantly higher for an inpatient compared to an outpatient (OR: 2.36; 95% CI: 1.09 to 5.11). No further evidence of associations with any other variables in univariate or multivariable analysis was seen.

Table 4. Regression analysis exploring the odds of medium or high dose antipsychotic use with reference to clinical and demographic characteristics for patients presenting to an EIP service.

		Univariate Analysis		Multivariable Analysis (n=142)	
	n	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Age	280	0.98 (0.95 to 1.01)	0.11	0.97 (0.93 to 1.01)	0.18
DUP (months)	154	0.97 (0.93 to 1.01)	0.09	0.98 (0.94 to 1.02)	0.23
GAF	276	1.00 (0.98 to 1.02)	0.81	0.99 (0.95 to 1.03)	0.50
SAPS	274	1.05 (0.96 to 1.14)	0.28	0.97 (0.82 to 1.15)	0.73
Sex	280				
Male		1.00		1.00	
Female		0.84 (0.45 to 1.57)	0.58	0.78 (0.28 to 2.14)	0.63
Treatment	280				
Outpatient		1.00		1.00	
Inpatient		**2.36 (1.09 to 5.11)**	**0.03**	2.83 (0.79 to 10.15)	0.11
Diagnosis	274				
Affective		1.00		1.00	
Schizophreniform		0.82 (0.39 to 1.73)	0.60	0.92 (0.29 to 2.98)	0.89
All other Diagnoses		1.83 (0.71 to 4.71)	0.21	2.17 (0.4 to 11.89)	0.37
Agitation Symptoms	290				
present [a]		1.00		1.00	
not present [b]		0.94 (0.49 to 1.78)	0.83	0.75 (0.26 to 2.17)	0.59

DUP= Estimated Duration of Untreated Psychosis
GAF = Global Assessment of Functioning
SAPS = Scale for Assessment of Positive Symptoms
[a] Score of 2=mild, 3=moderate, 4= marked or 5= severe on the SAPS excitatory/agitation score
[b] Score of 0= none or 1= questionable on the SAPS excitatory/agitation score

After one month of treatment the proportion of people in C2 requiring medium or high doses of medication increased from 17.9% to 42.7%. Of these, 4 patients (1.2%) were treated with doses above the BNF maximum, all of which were olanzapine at doses of 22.5 to 30mg per day.

Data on the dose of medication at both time points in C2 were available for 268 patients. Of these, 72 (26.8%) required an increase in dose over the first month of engagement with the early intervention service (Table 5). All of those who required an increase in dose had received an initial low dose of medication which was increased to a medium dose for 71 patients and a high dose for 1 patient. The dose of medication decreased for 10 (3.7%) people between initial assessment and following one month of engagement with the service. All 10 had been started on a medium dose of antipsychotic and the dose was reduced to a low dose over the first month. Medication was discontinued for one person who initially started on a low dose of medication. The dose for 186 people (69.4%) remained unchanged over the first month of engagement with the EIP service.

Table 5. Regression analysis exploring the odds of an increase in dose (compared with no increase - stay the same or decreased) with reference to clinical and demographic characteristics for patients presenting to an EIP service.

	Univariate Analysis			Multivariable Analysis (n=142)	
	n	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age	268	0.98 (0.96 to 1.00)	0.11	0.99 (0.95 to 1.03)	0.51
DUP (months)	147	0.99 (0.97 to 1.01)	0.37	1.00 (0.97 to 1.02)	0.76
GAF	263	0.97 (0.94 to 0.99)	<0.01	0.97 (0.93 to 1.01)	0.10
SAPS	262	1.13 (1.05 to 1.23)	<0.01	1.04 (0.89 to 1.21)	0.61
Sex	268				
Male		1.00		1.00	
Female		0.8 (0.46 to 1.40)	0.44	1.37 (0.57 to 3.29)	0.48
Treatment	268				
Outpatient		1.00		1.00	
Inpatient		2.10 (1.09 to 4.05)	0.03	1.76 (0.61 to 5.06)	0.30
Diagnosis	265				
Affective		1.00		1.00	
Schizophreniform		0.83 (0.43 to 1.61)	0.58	0.68 (0.23 to 2.01)	0.48
All other Diagnoses		1.13 (0.46 to 2.81)	0.79	1.43 (0.29 to 7.12)	0.67
Agitation Symptoms	263				
present [a]		1.00		1.00	
not present [b]		1.66 (0.95 to 2.91)	0.07	1.23 (0.5 to 3.06)	0.65

DUP= Estimated Duration of Untreated Psychosis
GAF = Global Assessment of Functioning
SAPS = Scale for Assessment of Positive Symptoms
[a] Score of 2=mild, 3=moderate, 4= marked or 5= severe on the SAPS excitatory/agitation score
[b] Score of 0= none or 1= questionable on the SAPS excitatory/agitation score

Univariate logistic regression analysis showed evidence that the odds of increasing a dose, compared to no increase (or a decrease), was significantly higher for an inpatient compared to an outpatient (OR: 2.10; 95% CI: 1.09 to 4.05, Table 5). Additionally, there was evidence of associations with GAF and SAPS. For every unit increase in GAF scale, the odds of an increase, compared to no increase, decreased (OR: 0.97; 95% CI: 0.94 to 0.99), and for every unit increase in SAPS the odds of an increase, compared to no increase, was 1.13 (95% CI: 1.05 to 1.23). However, they did not remain significant in the multivariable analysis. There was no further evidence of associations with any other variables in univariate or multivariable analysis (Table 5).

DISCUSSION

Summary of Findings

This study describes the pattern of antipsychotic prescribing for a naturalistic cohort of patients presenting for assessment of FEP in a geographically defined catchment over a 21 year period. The data demonstrate the changes over time in the choice of antipsychotic medication, the move towards predominantly second generation antipsychotic use and the prevalence of olanzapine as a first choice medication. Guidelines issued in both Europe and America widening the choice of antipsychotic medication or specifically not recommending olanzapine as an initial choice of agent do not appear to have had an impact on prescribing patterns. Additional indicators of good practice such as the use of low doses of antipsychotic medication for the initial treatment of FEP and the avoidance of high doses and antipsychotic polypharmacy are demonstrated. The demographic and clinical factors investigated did not appear to significantly influence the initial choice of antipsychotic medication. There was some evidence that inpatient treatment setting was associated with a higher initial dose of antipsychotic medication (>50% BNF maximum). Increasing dose requirements over the first month of engagement with an EIP service was associated with poorer global functioning at baseline, greater positive symptoms at baseline and the inpatient treatment setting. However, these associations were not seen in the multivariable model.

Comparison with Previous Literature and Clinical Implications

EIP services aim to provide timely access to comprehensive assessment and programmes of care including medical, psychological, occupational and social support.[29] A positive first experience of using antipsychotic medicines is likely to have an impact on future engagement with services and outcomes.[30 31] Careful consideration of the first antipsychotic medication involves balancing side effects with expected benefits and incorporating the patient perspective through a shared decision making approach. Managing side effects, is a significant challenge with the risks of metabolic abnormalities, sexual problems and movement disorders among the many potential disadvantages of using these medications. Given the variety of antipsychotic medication available, the lack of evidence for relative

efficacy benefits in FEP in the context of significant differences in side effect profiles,[12] it is useful to examine what medications are actually used in practice with clinical implications for the services' approach to managing physical health complications of antipsychotic use.

The trend towards SGA use over time in our study reflects the early optimism for medications with reduced propensity to cause anticholinergic side effects and long term movement disorders. While the preference for olanzapine as a first choice antipsychotic has been previously been reported in the literature.[32-35] the prescribing rate in this cohort are high by comparison. For example, a Spanish study of prescribing practices for FEP found that 22.7% were prescribed olanzapine and a UK study described a prescribing rate of 35%. In the United States ,where the PORT guidelines specifically exclude olanzapine as a first choice medication the prescribing rate was 31.2% in the Recovery After an Initial Schizophrenia Episode-Early Treatment Programme (RAISE-ETP) study.[20] Although this study did not explore the reasons for clinicians' choice of antipsychotic medication, olanzapine may be perceived to be more effective[36] and reduce the need for additional prescribing e.g. a benzodiazepine or hypnotic.

Olanzapine has a higher risk of inducing weight gain and metabolic abnormalities in comparison to other antipsychotics that could potentially be used as an initial treatment option in FEP.[37 38] Antipsychotic induced weight gain causes considerable patient distress, has serious general health implications and leads to early discontinuation of medication.[39] Over time the characteristics of the population changed with more people provisionally diagnosed with substance use disorder in comparison to the early cohort. This likely reflects the achievements of the EIP service in reducing DUP and the diagnostic criteria for schizophrenia requiring presence of symptoms for six months or more. Olanzapine is a sedative medicine and may be a reasonable choice if the patient were agitated, a presentation commonly associated with substance misuse. However, univariate and multivariate regression did not find an association with symptoms of agitation. While a reduction in the proportion of FEP patients using olanzapine as an initial treatment could be beneficial, strategies to prevent and manage weight gain should form part of an EIP programme where olanzapine continues to be used as a first line agent. Lifestyle interventions [40], metformin [41] or liraglutide [42] are potential options.

Historically LAI and depot formulations were recommended if adherence to oral medication was poor[13] or, in more recent times, as first line agents if the patient expressed a preference for the formulation.[43] The advantages may include reduced hospitalisation, more stable therapeutic blood levels with no additional side effect burden and, convenience for the patient.[43 44] Confirming adherence through the use of LAIs may lead to better treatment decisions and earlier recognition of treatment resistance. However, barriers to the use of these formulations include a reluctance on the part of some patients to engage in their use and a view that there may be a coercive nature to injecting medication.[45] In this study the prevalence of LAI use is low, with some historical use of the FGA's described in our first cohort. The preference for SGA's may have had an impact on the use of LAI's until the development of the first second generation LAI formulation of risperidone.

Clozapine is generally reserved for patients whose symptoms have not responded to adequate trials of two antipsychotic medication at the maximum tolerable dose.[13 46] When compared to chlorpromazine as an initial treatment for FEP, clozapine was no more effective.[47] However, early use of clozapine for those considered treatment resistant has been recognised as increasingly important. For example, early use of clozapine was effective for 75% of those with treatment resistance included in an observational study by Agid *et al*. Furthermore, Yoshimura *et al* report that early use of clozapine was associated with a response rate of 80% compared with a response rate of 30% if clozapine initiation was delayed by 2.8 years or more.[48] In our study none of the patients were treated with clozapine and this is likely due to the inclusion of patients in the very early stages of treatment with up to 30 days antipsychotic exposure at study entry. Additional research has demonstrated that the time to clozapine treatment for those with treatment resistant illness in our study cohorts is reducing with an average time to clozapine treatment of 6.7 years in the FEP study[49] compared with 2.1 years for those engaged in the EIP service.[50]

Guidelines recommend commencing antipsychotic medication at the lower half of the dose range in FEP.[16 17] We therefore took a pragmatic approach to describing the pattern of antipsychotic doses by expressing dose as a percentage of the BNF maximum. Guideline recommendations were generally adhered to with 78.6% of patients prescribed lower doses at initial presentation and the use of high dose medication regimens was negligible at both initial assessment and after one month of treatment. Bioque *et al* reported that 8.9% of

patients received higher doses of medication, by comparison.[34] Our description of antipsychotic use in the very early stages of treatment for FEP may explain the low rates of antipsychotic polypharmacy and high dose treatment strategies in comparison to other studies.[34 51]

Clinical practice guidelines in psychiatry are often difficult to implement.[21 52] In the RAISE-ETP study, for example, Robinson *et al* found that, at the point of engagement with an EIP service, medication review would be beneficial for 39.4% of the 404 patients enrolled in their study. The reasons for medication review included the use of olanzapine (31.2%) and the use of high dose regimens (8.8%) or combinations of antipsychotic medications (23.3%).[51]Proactive support for prescribing practice can be an effective means of improving the quality of medication use in first episode psychosis.[19 48 53] Observational studies by Yoshimura *et al* and Yeisen *et al* demonstrated that the initial choice of antipsychotic can be influenced by locally implemented algorithms.[48 53] Robinson *et al* developed the NAVIGATE prescribing principals and the COMPASS decision making tool which was designed to facilitate communication between the patient and the prescriber in the RAISE trial.[19] Training was provided for prescribers and they were given ongoing support throughout the study. Over a 2 year period study participants (n=223) had more medication visits, were more likely to use a medication that conformed to the NAVIGATE guidelines, experienced fewer side effects and gained less weight than those who has received usual community care (n=181). Adherence estimator scores also improved in the NAGIGATE group but not in the community group. The models of care for EIS internationally give varying attention to supporting medicines optimisation.[1] This evidence and the results of our study suggest that EIP services and patients could benefit from proactive support for prescribing practice.

Strengths, Limitations and Future Research

We report prescribing data from a naturalistic cohort with inclusion criteria reflecting the age range and diagnoses presenting to an EIP service. The longitudinal data allow a view of the pattern of prescribing practice over a 21 year period during the development and implementation of an EIP service. We were also able to describe the clinical use of the medications in terms of dose changes and the need to switch medication or formulation over the first month of engagement with the EIP service. In studies regarding antipsychotic use in an FEP population, patients were often treated with antipsychotic medication for a number of months before assessment by an EIP service and therefore may not accurately reflect the first choice of antipsychotic or initial dose.[32 34 35 51] In our study, participants had less than 30 days antipsychotic exposure.

Patient related factors other than those assessed, such as patient preference sociodemographic factors or clinical metabolic parameters, may have had an influence on the choice or dose of antipsychotic medication. While we were able to describe the choice of antipsychotic when switching medication, we did not have the data to explore the reasons for switching medication. The retrospective nature of this study led to some missing data in both cohorts. The pattern of prescribing in the interim period between the FES and the EIP studies could not be described. International prescribing guidelines are not specifically promoted in Ireland and there are no local antipsychotic prescribing guidelines for FEP in the Irish mental health services. Their influence may, therefore, be expected to be poor. It would be useful to examine the topic prospectively to include shared decision making processes and clinician related factors and investigate the impact on patient outcomes including physical health. Future local or national guidelines may influence prescribing practice and include decision support tools and proactive management protocols to mitigate the potential side effects of antipsychotic medication.

CONCLUSION

There is clearly a move toward the use of SGAs as initial treatment for FEP. Guidelines which recommend avoiding olanzapine as an initial choice based on its side effect profile, do not appear to have had an influence on prescribing practice. Antipsychotics are generally initiated at low doses. Given the importance of early experiences with medication consideration should be given to including a proactive approach to medicines optimisation within the EIP model of care. This could include locally agreed guidelines, decision support tools for both patients and clinicians and active management of side effects.

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CONTRIBUTIONS

DK designed and conducted the study in collaboration with JS and MC. DK extracted the data for the DETECT cohort from the DETECT research database and hospital prescribing records. RD and CB extracted the data in relation to the first episode study. DK analysed the data with advice from FB. DK wrote the manuscript with input from SMcW, FB, JS and MC.

COMPETING INTERESTS

The authors report no competing interests

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DATA SHARING STATEMENT

Anonymised participant data is held in a secure research server and will be handled in accordance with the ethical approval for this project.

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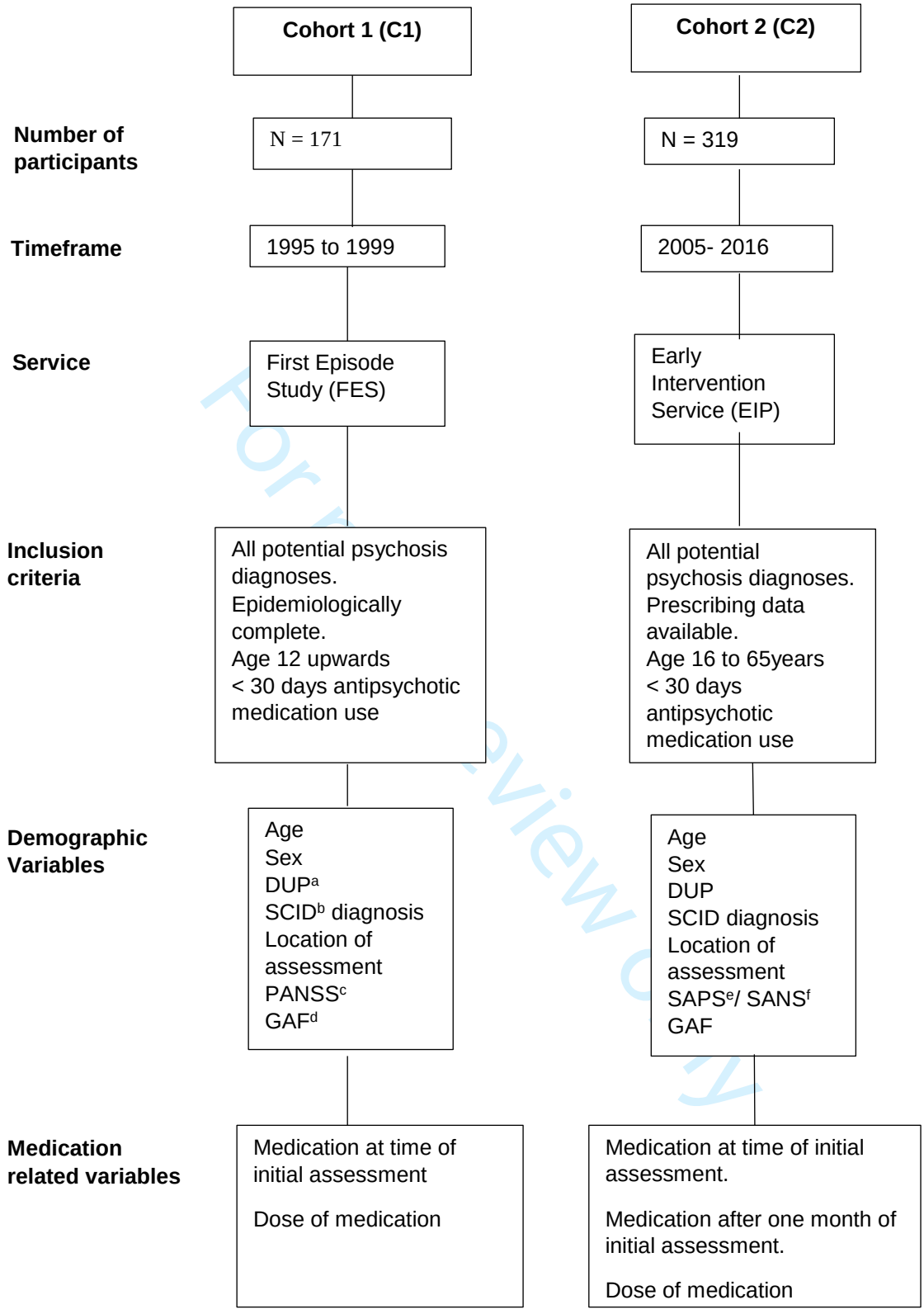
Figures

Figure 1. Description of cohorts of patients presenting to an early intervention service, timeframe of presentation, inclusion criteria, demographic and medication related variables

[a]Duration of Untreated Psychosis; [b]Structured Clinical Interview for Diagnosis; [c]Positive and Negative Symptom Scale; [d]Global Assessment of Functioning; [e]Scale for Assessment of Positive Symptoms; [f]Scale for Assessment of Negative Symptoms

Figure 2. Proportion of olanzapine (%) prescribed per year for patients presenting for assessment of first episode psychosis. Guidelines published in 2009 advising against the use of olanzapine as an initial medication in FEP and widening the choice to first or second generation antipsychotics (orange line).



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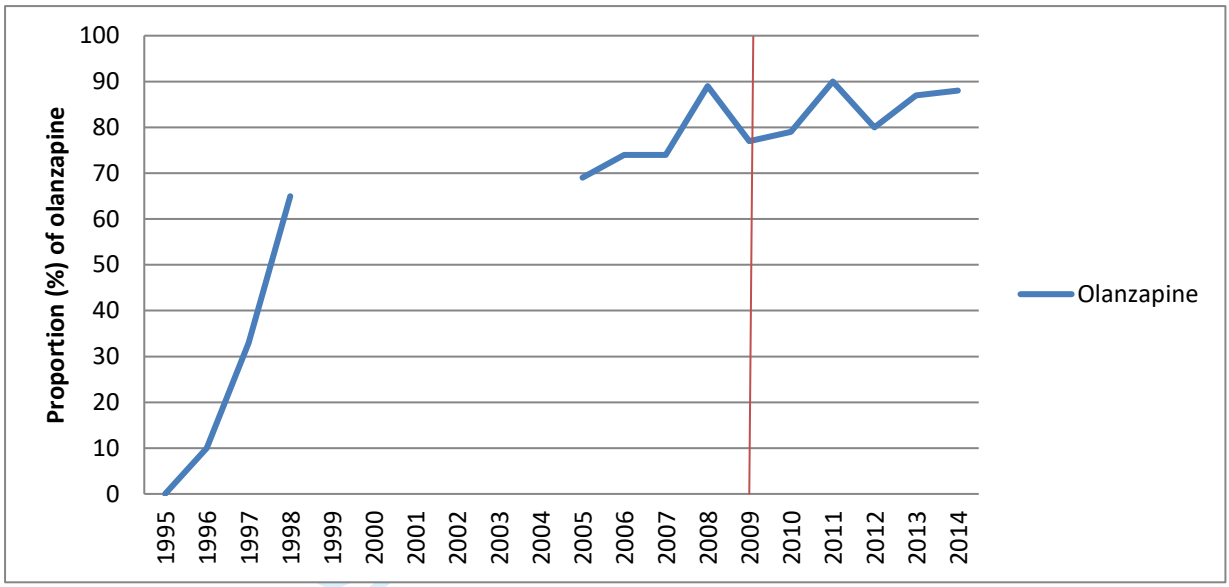

Figure 2 Proportion of olanzapine (%) prescribed per year for patients presenting for assessment of first episode psychosis

Guidelines published in 2009 advising against the use of olanzapine as an initial medication in FEP and widening the choice to first or second generation antipsychotics (orange line).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8,9
		(b) Give reasons for non-participation at each stage	8,9
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	10,11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-17
		(*b*) Report category boundaries when continuous variables were categorized	10-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.